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LETTER TO EDITOR

A case report of vaccine-induced immune thrombocytopenia and thrombosis syndrome after Ad26.COV2.S vaccine (Janssen/Johnson & Johnson)☆

Keywords SARS-CoV-2; COVID-19; Janssen; Vaccine; VITT syndrome; Thrombosis; Thrombocytopenia

Abbreviations

COVID	coronavirus disease
DIC	disseminated intravascular coagulation
FDPs	fibrin degradation products
ITP	immune thrombocytopenic purpura
MRI	magnetic resonance imaging
PCR	polymerase chain reaction
PF4	platelet factor 4
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TTP	thrombotic thrombocytopenic purpura
VITT	vaccine-induced immune thrombocytopenia and thrombosis

Introduction

Vaccine-induced immune thrombocytopenia and thrombosis (VITT) syndrome has recently been described after the ChAdOx1 nCoV-19 vaccine (AstraZeneca) [1]. This syndrome is characterized by the occurrence of venous and/or arterial thrombosis, often at atypical sites, with thrombocytopenia and positive anti-PF4 (platelet factor 4) antibodies, in a recent context of vaccination against coronavirus disease 2019 (COVID-19).

We describe here a case of VITT syndrome, which occurred following vaccination with Ad26.COV2.S vaccine (Janssen).

Case report

On August 2, 2021, ten days after receiving a dose of Ad26.COV2.S vaccine (Janssen/Johnson & Johnson), a 57-years-old man was admitted for left hemiplegia. The rest of clinical examination was unremarkable. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) testing by nasopharyngeal swab was negative. He has no significant medical history and does not take any long-term treatment. Ischemic stroke, of thromboembolic origin with description of a proximal occlusion of the right internal carotid artery, was confirmed on brain magnetic resonance imaging (MRI).

Initial blood tests were abnormal, including thrombocytopenia at 27 G/L, hepatic cytolysis at 10N and biological disseminated intravascular coagulation (DIC) with fibrinogen < 1 g/L, D-dimer> 128,000 ng/mL and fibrin degradation products (FDPs) > 150 μg/mL. Myelogram was normal.

Arterial Doppler ultrasound of the supra-aortic trunks confirmed a complete thrombosis of the right internal carotid artery. Ultrasound and abdomino-pelvic CT scan revealed partial portal vein thrombosis and right and middle hepatic vein thrombosis. Pain in the left leg prompted the realization of a venous Doppler ultrasound of the lower limbs, finding a distal deep venous thrombosis. Transthoracic echocardiography was normal.

Patient received intravenous acetylsalicylic acid (250 mg/24 h) and subcutaneous enoxaparin (100 IU/kg/12 h) and was admitted to the intensive care unit.

Neurological examination showed cognitive disorders, hemiparesis of the left upper limb rated at 1/5 and hemiparesis of the left lower limb side at 2/5, with signs of spatial neglect. Because of neurological worsening (appearance of a left homonymous hemianopsia at 48 hours), brain CT scan showed intracranial bleeding leading to stop antithrombotic agent and curative anticoagulation.

VITT syndrome was suspected. Differential diagnostics were ruled out (SARS-CoV-2 infection, others infections, immune thrombocytopenic purpura (ITP), drugs, hypersplenism, genetic disorder, cancer, trauma, surgery, immobilization, thrombotic thrombocytopenic purpura (TTP), thrombophilia). Search for anti-PF4 antibodies and a platelet aggregation test were performed, from which only anti-PF4 antibodies returned positive at 1,181 IU/L (N < 0.5) by ELISA method (Zymutest HIA IgGAM Hyphen), platelet aggregation test returned normal.

The patient received corticosteroids 0,75 mg/kg and intravenous immunoglobulins at 2 g/kg over 2 days, either seven days after the onset of symptoms. Biological parameters improved over the next few days, in particular platelets (Fig. 1) and fibrinogen which returned to normal values in 5 days and liver function tests in 17 days. On day 10, internal carotid artery was re-permeabilized on arterial Doppler ultrasound, and thrombus completely disappeared on the control a month and a half later.

☆ This case has been declared to the French National Pharmacovigilance Database on August 9, 2021 under number SE20212123.

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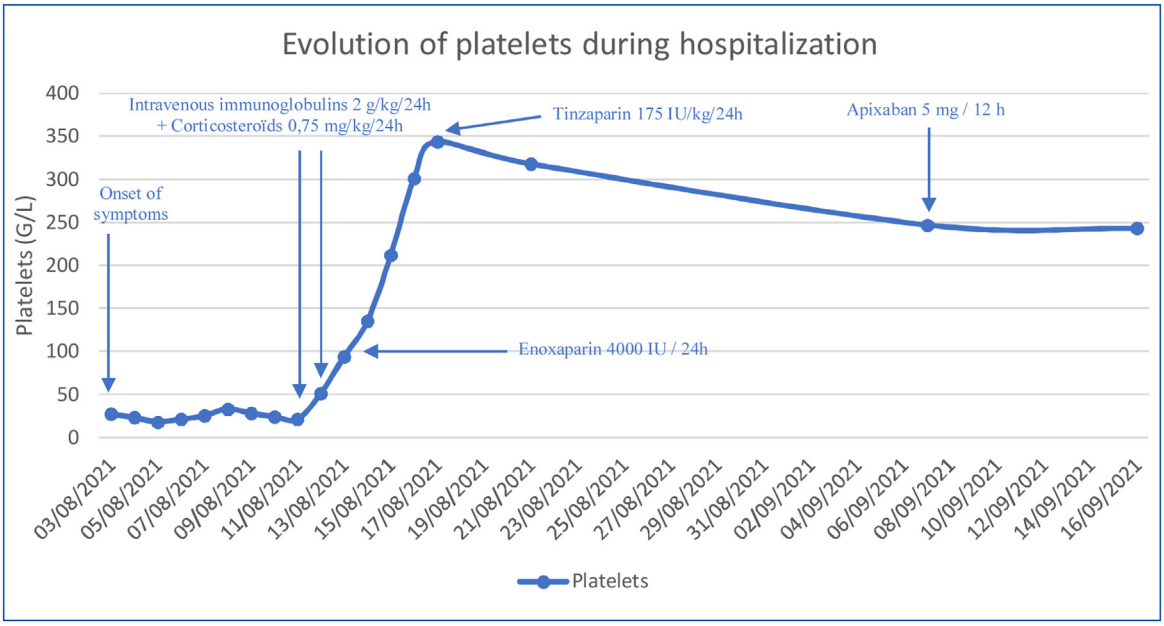

Figure 1. Evolution of platelets during hospitalization.

Concomitantly, neurological symptoms began to improve, including hemiplegia, cognitive and ophthalmologic disorders. Follow-up brain scan did not show any new intracranial bleeding. Preventive anticoagulation by subcutaneous enoxaparin 4000 IU/24 h was reinitiated, followed by subcutaneous tinzaparin 175 IU/kg/24 h and later by Apixaban 5 mg/12 h, once the liver function is normal.

Seven days after initiation of treatment, neurological examination improved, with hemiparesis of the left upper limb rated at 3/5 and hemiparesis of the left lower limb rated at 4/5.

Two months after the onset of symptoms, neurological examination objectified hemiparesis of the left upper limb rated at 4/5 and hemiparesis of the left lower limb rated at 4/5.

Four months after the onset of symptoms, patient can walk a short distance with a cane.

Discussion

According to us, this is the first case of VITT syndrome reported to the French Regional Pharmacovigilance Centers in France for the Ad26.COV2.S vaccine (Janssen/Johnson & Johnson). A declaration to the French National Pharmacovigilance Database was made on August 9, 2021 and was registered under number SE20212123. Causality relationship between Ad26.COV2.S vaccine (Janssen/Johnson & Johnson) and VITT syndrome was assessed as ''likely'' (I3, C2S3) with the French pharmacovigilance causality [2]. The latest report of pharmacovigilance of ChAdOx1 nCoV-19 (AstraZeneca) on November 25, 2021 described 29 cases of confirmed VITT in France *vs* 4 cases for the Ad26.COV2.S vaccine (Janssen/Johnson & Johnson) [3].

The diagnosis of VITT is definite according to the consensus of the UK Haematology Expert Group [4] with a delay of onset of symptoms of 10 days after vaccination, multiple thrombosis even if the sites described are not the most frequent, biological assessment with a major DIC (D-dimer > 4000 ng/mL, platelets at 27 G/L) having been resolved few days after initiation of immunoglobulins and corticosteroids and positive anti-PF4 antibodies ELISA assay.

Our research in the literature found several studies concerning mainly ChAdOx1 nCoV-19 (AstraZeneca) on this syndrome in the United States and in Europe in particular in the United Kingdom, in Denmark, in Norway, in Austria and in Germany. Locations described as being the most frequent were cerebral veins, pulmonary arteries and multiple sites [4]. Although similar, there are differences between VITT syndrome induced by ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.COV2.S vaccine (Janssen/Johnson & Johnson): in particular median time to onset of, respectively, 10- and 16-days post-vaccination and lower D-dimer levels in Ad26.COV2.S vaccine recipients [5]. There would also be more intracerebral hemorrhages after Ad26.COV2.S administration (Janssen/Johnson & Johnson) [5]. These differences are important to consider in the diagnostic process of VITT syndrome. Incidence was around 1/50,000-100,000 for both vaccines [4,6] but there is a higher incidence of ChAdOx1 nCoV-19 (AstraZeneca) in the United Kingdom, a country where this vaccine was mainly used, unlike in the United States where Ad26.COV2.S vaccine (Janssen/Johnson & Johnson) is the majority. The fact that the incidence of occurrence of VITT syndrome is lower in recipients of Ad26.COV2.S vaccine (Janssen/Johnson & Johnson) may be explained by the later release and by less use than other vaccines.

Treatments were variable and mainly included corticosteroids and intravenous immunoglobulins. Other treatments have been tested, specifically rituximab (anti-CD20) and eculizumab (anti factor C5) [7], the principle remaining of slowing down immune response [7]. It was not recommended to have recourse to platelet transfusions except to cover any possible procedures, as this would promote aggravation of thrombosis [4,8].

Mortality reported in the literature varied from 23% to 72% depending on the existence or not of intracranial bleeding and thrombocytopenia < 30 G/L [4,5], and also associated with early diagnosis and rapid initiation of appropriate treatment. A predictive mortality score has been developed: the FAPIC score [9]. It includes fibrinogen (< 1,5 g/L), age (≤ 60 years), platelet count (< 25 G/L), intracerebral hemorrhage and cerebral venous thrombosis, and can be used to predict mortality of VITT syndrome [9].

In our patient's case, platelets normalized quickly after initiation of treatment. Due to the description of a non-heparin-dependent pathophysiological mechanism [8], we anticoagulated the patient with heparin treatment, and this did not cause a significant drop in platelets, which remained at a normal level.

Conclusion

As of 10 November 2021, there have been more than 7 billion doses of vaccine worldwide and currently available vaccines have been extensively tested in clinical trials and their efficacy and safety is well established. Common vaccine-related side effects are fever, myalgia, arthralgia and headache [8]. Occurrence of serious adverse events attributable to the vaccine therefore remains difficult to interpret. VITT syndrome has only been reported very few times in the literature [1,4,6,8—10], around 474 cases for the ChAdOx1 nCov-19 in European Union and United Kingdom on October 9, 2021, and 28 cases for the Ad26.COV2.S vaccine in USA on July 19, 2021. Risk-benefit ratio remains in favor of vaccination, in particular since SARS-CoV-2 infection is more thrombogenic than vaccination [6].

Link between occurrence of VITT syndrome and adenovirus-vector-based SARS-CoV-2 vaccines is increasingly established, but this event remains rare and it therefore appears essential to identify the VITT syndrome early on: implementation of rapid treatment allows almost immediate clinical improvement and would therefore reduce mortality of this extremely serious adverse event.

Disclosure of interest

The authors declare that they have no competing interest.

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