Thrombosis and Thrombocytopenia Syndrome Causing Isolated Symptomatic Carotid Occlusion after Covid-19 Vaccine

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Introduction

Thrombosis with thrombocytopenia syndrome (TTS) is a rare adverse event described after vaccination against COVID-19, mainly with nonreplicant adenovirus vector-based vaccines. As of September 9, 2021, reported cases of TTS in Europe and United States account for 8.5 per million doses with ChAdOx1 nCov-19 (AstraZeneca), 3.1 with Ad26.COV2.S (Janssen/Johnson&Johnson), 0.4 with BNT162b2 (Pfizer/BioNtech), and 0.01 with mRNA-1273 (Moderna).[1–3] Its main features are the presence of acute arterial or venous thrombosis, severe thrombocytopenia, elevated D-dimer, and demonstration of platelet factor 4 (PF4) antibodies in the first 42 days after vaccination.[4–6] TTS is usually associated to a severe thrombosis profile, affecting multiple organs, most frequently cerebral venous sinus, splanchnic veins, and deep veins with pulmonary embolism. We describe an illustrative case of isolated thrombosis of the carotid artery causing stroke with mildly altered laboratory parameters. The patient provided written informed consent for this report.

Case Presentation

A 46-year-old man presented with repeated episodes of amaurosis fugax. His medical history included smoking and hypertriglyceridemia and had received a single dose of Ad26.COV2.S (Janssen/Jonhson&Johnson) COVID-19 vaccine 14 days before symptom onset. He had no history of heparin exposure. Vital signs, ophthalmologic, and neurological examination were unremarkable. Laboratory tests showed mild thrombocytopenia (125,000/μL), with normal D-dimer and fibrinogen levels (►**Fig. 1**). Computed tomography (CT) angiogram showed a floating thrombus in the left carotid bulb, followed by nonattenuation of the internal carotid artery (ICA), with adequate filling of the circle of Willis (►**Fig. 2**) and without signs of atheromatosis or other vascular abnormalities. Rapid assay screening test for PF4-heparin antibodies resulted negative. No urgent revascularization procedures were performed, the patient was admitted to the stroke unit and anticoagulation with fondaparinux (7.5 mg sc/day) was initiated on day 1 after confirmation of thrombocytopenia (136,000/μL). Enzyme-linked immunosorbent assay (ELISA) testing for PF4 antibodies (AESKULISA HiT II) was reported positive on day 2, with high optical density values (2.054, cut off 0.494), and 0.5 mg/kg/day intravenous immunoglobulin (IVIG) was administered for 2 days. Testing for other hypercoagulable states (antiphospholipid syndrome, genetic disorders) were negative. Electrocardiogram monitoring was unremarkable. Transthoracic echocardiography showed no structural abnormalities, and injection of agitated saline demonstrated occasional late bubble transit only after Valsalva maneuvers, compatible with slight right-to-left shunt although no atrial septum defects were visualized. After cardiology consultation, this finding was considered as a small incidental patent foramen ovale of low embolic risk and highly unlikely related to the carotid thrombus. Heparin-induced platelet activation tests were negative. A contrast-enhanced body-CT ruled out thrombosis in other organs. New ELISA tests (Asserachrom HPIA) showed persistently high positive results on

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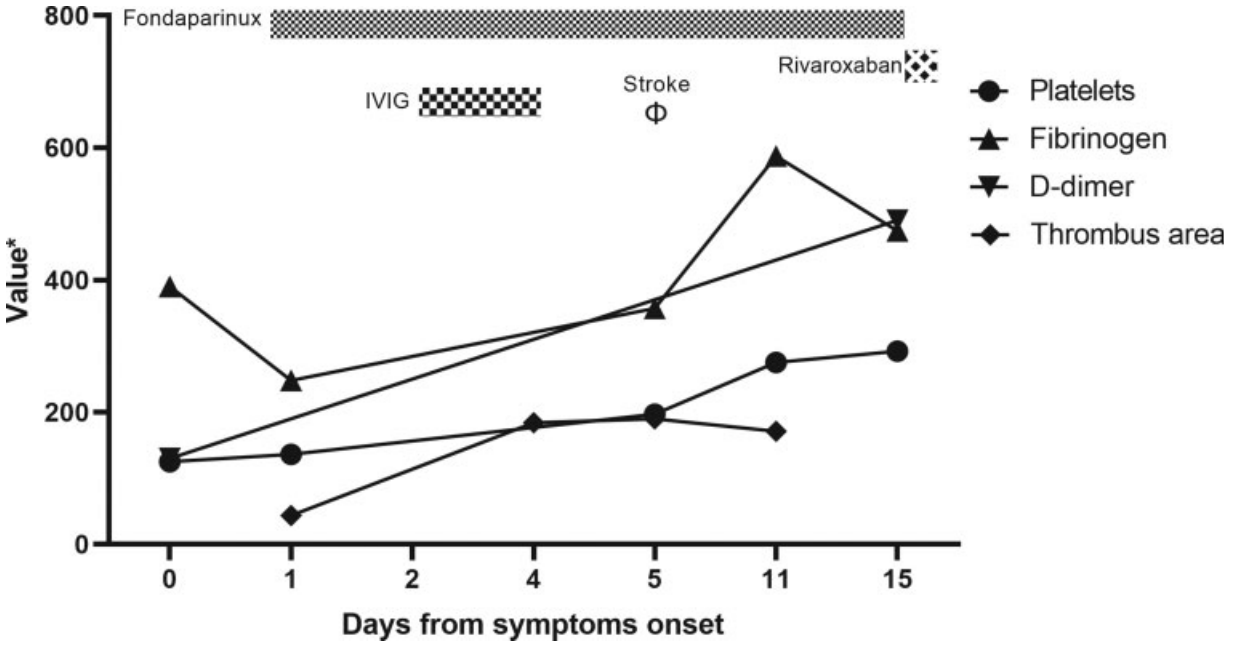

Fig. 1 Timeline of events, laboratory, and ultrasound tests. *Platelets $\times 10^3/\mu L$, fibrinogen mg/dL, D-dimer ng/mL, thrombus area mm^2 in carotid ultrasound (longitudinal plane).

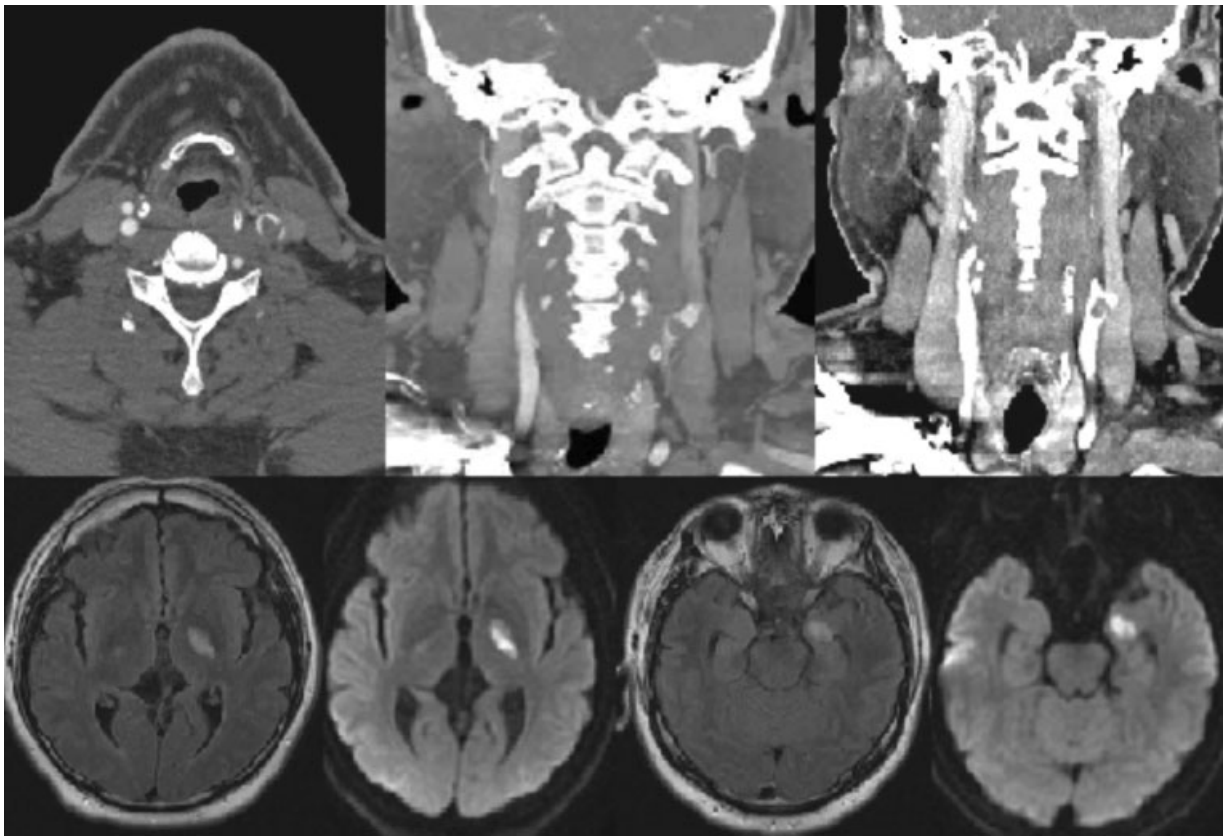

Fig. 2 Initial computed tomography (CT) angiogram (up) showing floating thrombus in left carotid bulb. Brain magnetic resonance (down) showing hyperintense lesions in fluid-attenuated inverse recovery and diffusion-weighed imaging compatible with acute infarction of anterior choroidal artery.

hospitalization days 4 and 8 (optical density 3.735 and 3.437, respectively, cutoff 0.905). Ultrasound monitoring of the carotid bulb showed thrombus growth in the successive days, despite treatment with IVIG and fondaparinux (►**Video 1**). On day 5, the patient referred blurry speech and right arm weakness. Magnetic resonance imaging showed signs of acute infarction of the anterior choroidal artery (AChA). By that time, platelet count had returned to normal (197,000/µL), thus treatment remained unchanged. The patient improved in the subsequent days. On discharge, fondaparinux was switched to rivaroxaban 20 mg/day.

Video 1.

Thrombus growth in carotid bulb. Online content including video sequences viewable at: https://www.thieme-connect.com/products/ejournals/html/10.1055/a-1674-0341.

Discussion

TTS is a serious adverse event of COVID-19 vaccines. PF4 antibodies seem to be the mainstay of its pathogenesis, by triggering massive platelet activation, aggregation, and consumption, resulting in thrombosis and reduced platelet count.[7] Although typical of heparin-induced thrombocytopenia (HIT), PF4 antibodies have also been described in healthy patients unexposed to heparin. A retrospective study of 4,000 blood donors found a prevalence of PF4 antibodies of 5%.[8] However, most patients with TTS have showed high optical densities compared with only 0.05% of healthy patients.[9,10] In a recent analysis of 93 patients with cerebral venous sinus thrombosis (CVST) before the COVID-19 pandemic, none had positive PF4 antibodies.[11] In contrast to HIT, rapid PF4-heparin antibodies assays have low sensitivity for TTS and should not be used.[12]

Neurological complications of TTS are mainly due to CVST and/or cerebral hemorrhage. We found 15 case descriptions of ischemic stroke, all affecting large anterior cerebral arteries (terminal ICA and middle cerebral artery), and most requiring mechanical thrombectomy and/or decompressive craniectomy.[13–22] Underlying atherosclerotic disease was uncommon, suggesting an embolic origin. Another series included 17 patients with unspecified ischemic stroke.[23] Most patients had severe thrombocytopenia and thrombosis of other organs. Three cases had mildly altered laboratory parameters on admission.[15,18,22] Floating carotid thrombus is an unusual finding present in only 1.5% of all stroke patients,[24] yet another case associated with TTS has been recently reported.[22] TTS case definition is constantly evolving but mostly requires significantly altered laboratory parameters. Highly elevated D-dimer has recently been included as a necessary criterion in some guidelines,[25] while others consider it a minor criterion.[4,6] Unfortunately, PF4 platelet activation assays were not available in our setting, nevertheless confirmed PF4 antibodies with high optical densities strongly supports TTS. This should raise questions about whether TTS should be suspected in a wider spectrum of recently vaccinated patients with unexpected thrombosis and almost normal laboratory parameters. It is also possible that the identification of thrombosis in some patients occurred in later stages of TTS when coagulation parameters were spontaneously returning to normal. Anticoagulation and IVIG are the mainstay of TTS treatment. In the present case, a slight increase in platelet count was noted after treatment although early treatment did not prevent thrombus growth and AChA infarction from occurring. It cannot be determined whether it was a hemodynamic phenomenon or an embolus coming from the proximal thrombosis of the ICA, being the latter one of the most frequent causes. Although initiation of fondaparinux may have played a role, anticoagulation has shown to be safe in the management of free-floating carotid thrombi.[24] Despite a slight right to left shunt was observed during agitated saline injection after Valsalva maneuvers, we consider highly unlikely to be related to the carotid thrombosis because of its size and the absence of signs of venous thrombosis. Current recommendations include anticoagulation for at least 3 months after diagnosis of TTS, as in other cases of provoked venous thrombosis. However, it remains unclear whether anticoagulant treatment should be continued (and for how long) after normalization of laboratory parameters.

We conclude that arterial thrombosis in close temporal relationship with adenovirus vector-based COVID-19 vaccines should be investigated as a possible case of TTS even in absence of significantly altered laboratory parameters. Further investigations are needed to determine the adequate therapy for these patients.

Conflict of Interest
None declared.

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