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Letter to the Editors-in-Chief

Long VITT: A case report

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ABSTRACT

Vaccine-induced immune thrombotic thrombocytopenia (VITT) has been described following adenovirus vector-based COVID-19 vaccines. This condition is associated with important morbidity and mortality following thrombosis related complications. Diagnosis is confirmed based on results of platelet factor 4 ELISA detecting anti-PF4 antibodies and of platelet-activation assay. Initial treatment strategy has been established but long-term management and follow up remain unclear. Most platelet-activation tests become negative after 12 weeks.

We describe a case of VITT which can now be characterized as long VITT. The patient initially had a lower limb ischemia, pulmonary embolism and cerebral vein thrombosis. He was treated with prednisone, intravenous immunoglobulin, argatroban and had a lower limb revascularization surgery. Rivaroxaban was then initiated for the acute treatment and continued for the secondary prevention of recurrent events. The patient still demonstrates positive platelet-activation tests and thrombocytopenia after more than 18 months of follow-up. No recurrent thrombosis or bleeding event have occurred. He is not known for any relevant past medical history other than alcohol consumption and slight thrombocytopenia (130 $\times$ 10^9/L since 2015). It is unclear if the ongoing and more important thrombocytopenia could be explained by the persistent platelet-activating anti-PF4 antibodies or the patient's habits.

Managing long VITT is challenging considering uncertainty regarding risks and benefits of long-term anticoagulation and potential needs of additional treatment. Additional data is needed to offer optimal long-term management for this patient population. We suggest that long VITT diagnosis definition might include the persistence within patient serum/plasma of anti-PF4 platelet-activating antibodies with clinical manifestations (e.g., thrombocytopenia) for more than 3 months.

Vaccine-induced immune thrombotic thrombocytopenia (VITT) has been described following adenovirus vector-based COVID-19 vaccines. This condition, similar to autoimmune heparin induced thrombocytopenia, is associated with important morbidity and mortality following thrombosis related complications [1]. Diagnosis is confirmed based on results of platelet factor 4 ELISA (PF4-ELISA) detecting anti-PF4 antibodies and of platelet-activation assay such as the serotonin-release assay with added PF4 (PF4-SRA). Initial treatment strategy has been established but long-term management and follow up remain unclear [2]. Most platelet-activation tests become negative after 12 weeks [3]. However, a case of VITT with platelet activation persistence at 3 months following the initial diagnosis and characterized by recurrent thrombocytopenia and death due to intracranial bleeding, was previously reported [4]. Similarly, other investigators have also reported another case with recurrent episodes of thrombocytopenia and positive PF4-SRA over a 9-month follow-up period [5]. Interestingly, the platelets-activation test and PF4 antibodies positivity fluctuated over time. Negative testing may have been the result of concurrent intravenous immunoglobulin (IVIG) treatments. Hence, it is unclear if patients with "long VITT" and persistent platelet activation are deemed at higher risk of recurrent thrombocytopenia, thrombosis and/or bleeding and if anticoagulation is still indicated.

We have previously published a case of VITT which can now be characterized as long VITT [6]. The patient initially had a lower limb ischemia, pulmonary embolism and cerebral vein thrombosis. He was treated with prednisone, IVIG, argatroban and had a lower limb revascularization surgery. Rivaroxaban was then initiated for the acute treatment and continued for the secondary prevention of recurrent events. The patient still demonstrates positive platelet-activation tests (performed at the McMaster Platelet Immunology Laboratory) and thrombocytopenia after more than 18 months of follow-up (Table 1). We also have observed one transient negative PF4-ELISA (Polyspecific anti-PF4 immunoassay, Immucor) result after 58 weeks of follow-up. However, PF4-SRA was not performed. PF4-ELISA was reported positive again ten weeks afterwards (Table 1). No recurrent thrombosis or bleeding event have occurred and no IVIG were needed beyond initial hospitalization. However, the patient is still unable to work because of a chronic ischemic neuropathy. He is not known for any relevant past medical history other than alcohol consumption (five per day) and slight thrombocytopenia (around 130 $\times$ 10^9/L since 2015). It is unclear if the ongoing and more important thrombocytopenia could be explained by the persistent platelet-activating anti-PF4 antibodies, another condition (none were identified, such as cirrhosis, portal hypertension, splenomegaly, viral hepatitis, antiphospholipid syndrome, etc.) or the patient's habits. D-dimer monitoring was not routinely performed beyond 19 weeks following the diagnosis of VITT given the favorable clinical evolution, ongoing anticoagulation and the relative stability of the thrombocytopenia.

Managing long VITT is challenging considering uncertainty regarding risks and benefits of long-term anticoagulation for secondary

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Table 1
Anti-PF4 and PF4-SRA persistence overtime.

	Since 2015	At dx in 2021	2 weeks after IVIG	6 weeks after dx	10 weeks after dx	16 weeks after dx	19 weeks after dx	22 weeks after dx	28 weeks after dx	41 weeks after dx	50 weeks after dx	58 weeks after dx	68 weeks after dx	79 weeks after dx
Anti-PF4, optical density		2.13	1.85	1.59	1.45	1.10		1.72	1.43	1.76	2.14	0.23	0.91	1.37
PF4-SRA		+		+					+		+		+	+
Platelet count $\times 10^9$/L	128–133	58	129	95	103	86	96			93		86	120	118
D-dimer, μg/L		16,561	1910	307	254	445	215							

dx indicates diagnosis.

prevention of recurrent events and potential needs of additional treatment such as IVIG if thrombocytopenia worsens. Additional data is needed to offer optimal long-term management for this patient population. We suggest that long VITT diagnosis definition might include the persistence within patient serum/plasma of anti-PF4 platelet-activating antibodies with clinical manifestations (e.g., thrombocytopenia) for more than 3 months. Clinical manifestations including recurrent thrombosis event, persistent thrombocytopenia, D-dimer or other hypercoagulability markers elevation need to be better described and included in future studies to tailor the long VITT spectrum definition.

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CRediT authorship contribution statement

All authors contributed to writing of the manuscript and approved the final version.

Conflict of interest

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