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by Andrew B. Song and Hanny Al-Samkari

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Adenovirus-associated thrombosis and thrombocytopenia: an emerging anti-PF4 disorder

Andrew B. Song, Hanny Al-Samkari

Division of Hematology Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Address correspondence to:

Hanny Al-Samkari, M.D.

Division of Hematology

Massachusetts General Hospital

55 Fruit St.

Bartlett Hall Extension Office 133

Boston, MA 02114

hal-samkari@mgh.harvard.edu

Phone: 617-643-6214

Fax: 617-643-8840

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In this issue of *Haematologica*, Uzun and colleagues illustrate a rare case of adenovirus infection associated with thrombocytopenia, cerebral venous sinus thrombosis, and heparin-independent anti-platelet factor 4 (PF4) antibodies[1].

In classic heparin-induced thrombocytopenia (HIT), negatively charged heparin molecules charge neutralize and facilitate close approximation of positively charged PF4 tetramers while causing neo-antigen sites to form on two ends of the PF4 tetramer. Heparin-dependent anti-PF4/heparin complex antibodies subsequently bind to these sites on platelet membranes and elicit FcγIIa receptor-mediated platelet activation, thrombocytopenia, and thrombosis. In contrast, vaccine-induced immune thrombocytopenia and thrombosis (VITT) involves heparin-independent antibodies targeting the heparin-binding domain of PF4, distinct from those in classic HIT[2].

VITT was first characterized in 2021 during the COVID-19 pandemic in association with the two adenovirus vector vaccines ChAdOx1 nCoV-19 and Ad26.COV2 and has subsequently garnered substantial global health interest[3]. VITT is a particularly severe anti-PF4 disorder with most patients experiencing symptomatic thrombotic complications, often in otherwise unusual sites such as splanchnic vein thrombosis and cerebral venous sinus thrombosis (CVST). Despite occurring in only 1-2 per 100,000 people in the general population annually and being a rare occurrence with HIT, CVST is the most common thrombotic complication of VITT, occurring in 25-60% of such patients[2, 4].

The patient presented by Uzun and colleagues had not received an adenovirus vector vaccine but instead had an adenovirus infection subsequently leading to severe thrombocytopenia, CVST, and an antibody profile analogous to that of VITT. PF4/heparin enzyme immunoassay (EIA) showed a strong response which is consistent with the high sensitivity of IEA assays for both HIT and VITT antibodies. A major

diagnostic branchpoint here was that a heparin induced platelet activation (HIPA) assay with low heparin concentration was negative, making classic HIT unlikely, whereas a modified assay with addition of exogenous PF4 was positive (PF4-enhanced HIPA or PIPA). These results are consistent with a VITT-like profile. Two additional patients have recently been described with adenovirus infection, thrombotic events (one with CVST), and VITT-like antibody profiles[5].

Improved recognition and diagnosis of this clinical entity is important due to the different treatment paradigms for VITT (and VITT-like disorders) versus classic HIT. Guidelines for treatment of VITT recommend the use of intravenous immunoglobulin (IVIG)[6], and mechanistically IVIG has been shown to inhibit FcγIIa-mediated platelet activation and subsequent thrombocytopenia and thrombosis. Uzun and colleagues' patient with adenovirus infection demonstrated significant improvement in platelet count and clinical stabilization with high-dose IVIG. Subsequently, ex vivo analysis of the patient's serum demonstrated the ability to induce procoagulant platelet formation along with abrogation by IVIG. This case, along with the others that have been published, suggests that adenovirus-associated thrombosis and thrombocytopenia syndrome with a consistent VITT-like antibody profile could be managed similarly to VITT. This may be particularly relevant in cases of severe and unusual thrombosis like CVST requiring urgent treatment.

Although typically contraindicated in HIT, heparin was used for anticoagulation in this patient due to initial concern for ITP rather than HIT. The patient did well and did not experience rebound thrombocytopenia after heparin exposure. This observation is consistent with existing data suggesting that heparin is safe and effective for anticoagulation in VITT. Additionally, heparin has been shown to inhibit binding of VITT anti-PF4 antibodies to their culprit heparin-binding site[7]. Given that both VITT and

adenovirus-associated thrombosis and thrombocytopenia are newly recognized clinical entities, clinicians may appropriately have reservations about usage of heparin given that these are PF4 disorders. This case is illustrative of the importance of better understanding the nuances of the pathophysiology unique to each PF4 disorder to facilitate optimal management of these life-threatening disorders.

What implications do these VITT-like manifestations of adenovirus infection and the ChAdOx1 nCoV-19 and Ad26.COV2 vaccines have on the future safety analyses and development of adenovirus-based vaccines such as those being developed for influenza, Ebola, Zika, malaria, and others? One recent meta-analysis of clinical trial of adenovirus vector-based vaccines did not observe a class-wide effect towards either thrombocytopenia or coagulopathy/thrombotic events in the general populations or in the pregnant population, although more prospective data is needed[8]. Further data characterizing any potential association between other viral infections/vectors with a thrombosis and thrombocytopenia syndrome would be helpful, although the fact that VITT itself is a recently discovered phenomenon, along with understanding of its PF4 antibody profiles, limits the ability of retrospective research to potentially associate this pathophysiology as a complication of other viral infections and better understand its actual incidence in adenoviral infections. It is interesting to note that a VITT-like syndrome was recently described in a patient after a human papilloma virus vaccine[9]. And although cases of VITT have been reported with the mRNA-based COVID-19 vaccines, these have been much rarer on an epidemiological scale.

Recent data from Warkentin and colleagues shows that sera obtained from selected patients prior to the COVID-19 pandemic demonstrated VITT-like characteristics[10]. These patients were identified by history of thrombocytopenia and/or thrombosis with strong reactivity in anti-PF4/heparin IgG EIA but negative HIPA and a significant

percentage subsequently tested positive by newer rapid anti-PF4 assays. The authors convey that this VITT-like antibody signal temporally could not have been associated with COVID-19 or COVID-19 directed adenovirus vector-based vaccines. The greater understanding of this clearly rare but severe complication of adenoviral infection (and possibly other viral infections) contributed by the case published by Uzun and colleagues is valuable, and reminds us that we must consider the possibility of a rare anti-PF4 disorder in patients with apparent thrombosis and thrombocytopenia syndrome but without antecedent heparin exposure.

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