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CASE REPORT

A cluster of pediatric vaccine-induced immune thrombotic thrombocytopenia–like cases with thrombosis and thrombocytopenia following respiratory infections—case series

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Abstract

Background: Adenoviral vector COVID-19 vaccine-induced immune thrombotic thrombocytopenia (VITT) is a heparin-independent platelet-activating disorder. An increasing number of VITT-like disorders without previous vaccination are being identified.

Key Clinical Question: To explore the association of the pediatric cluster of post-infectious thrombosis and thrombocytopenia with VITT-like disorders.

Clinical Approach: Three children with severe thrombocytopenia, coagulopathy, elevated D-dimer, and thrombotic events (cerebral venous sinus thrombosis) were reported. Two had positive nasopharyngeal samples for adenovirus, and 1 had group A streptococcus infection. They all had a COVID-19 history and low-risk antiphospholipid syndrome. Heterozygosity for factor V Leiden was found in 2 children. In 2 patients for whom anti–platelet factor 4 (PF4) serology was performed, positive results were found by PF4/polyanion lateral-flow immunoassay but negative results by PF4/polyanion chemiluminescence immunoassay. All patients were treated with enoxaparin or fondaparinux and intravenous immunoglobulin, while 3 received platelets transfusion and steroids.

Conclusion: This cluster of pediatric cases with thrombosis and thrombocytopenia may indicate a postinfectious (most notably, postadenovirus) VITT-like disorder.

KEYWORDS
adenovirus, antiphospholipid syndrome, cerebral thrombosis, COVID-19, streptococcus, thrombocytopenia, VITT-like disorder

Dimitra Dimopoulou, Lida Mentesidou, Vana Spoulou, and Helen Pergantou contributed equally to this study.

Essentials

- A rising number of vaccine-induced immune thrombotic thrombocytopenia (VITT)–like cases are being identified.
- We present children with thrombosis and thrombocytopenia following respiratory infections.
- This cluster of children may indicate a postinfectious (adenovirus) VITT-like disorder.
- Larger cohort studies are needed to determine a possible link of VITT-like cases with COVID-19.

1 | INTRODUCTION

Thrombosis is rare in children, ranging from 0.07 to 0.14 per 10,000 children under 18 years per year before COVID-19 [1]. However, an increase in complications related to coagulation abnormalities after COVID-19 was reported, particularly in patients with risk factors for thrombogenesis, such as antiphospholipid syndrome (APS) or infection [2–4]. Platelet-activating antibodies against platelet factor 4 (PF4), including heparin-induced thrombocytopenia (HIT) and adenoviral vector SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia (VITT), could be another cause of prothrombotic disorders. An increasing number of VITT-like disorders without previous vaccination are being identified [5,6].

To date, data about COVID-19 or other respiratory infections related to thrombosis in children are limited [7]. We present a case series of children <16 years old who were admitted to a tertiary pediatric hospital in Greece due to thrombotic disorders (cerebral venous sinus thrombosis [CVST]) and thrombocytopenia, with elevated SARS-CoV-2 antibodies, all following respiratory infections caused by adenovirus or group A streptococcus.

2 | CASE SERIES

The demographics, clinical features, laboratory/neuroimaging findings, and treatment of all cases are summarized in the Table.

2.1 | Case 1

An 8-year-old previously healthy female residing in Athens was admitted in May 2023 due to acute severe frontal headache, somnolence, and vomiting, presenting 2 days prior to hospitalization. Mild acute COVID-19 infection was reported 1.5 months ago, and upper respiratory viral infection was reported 1 week ago; elevated anti–SARS-CoV-2 immunoglobulin (IgG; 328AU/mL) was found. On admission, the child was afebrile with mildly decreased level of consciousness and otherwise normal neurologic evaluation. Laboratory examination revealed thrombocytopenia (platelet count, 50×10^9/L, nadir level), hypofibrinogenemia (88 mg/dL, nadir level), reduced factor (F)VII levels (49 U/dL), and increased D-dimer (>36 μg/mL, highest level; Innovance, Siemens Healthineers), while international normalized ratio (INR) was 1.1 (highest level, 1.5). Polymerase chain reaction for adenovirus was positive in the nasopharyngeal sample. Brain magnetic resonance imaging (MRI)–magnetic resonance angiography–magnetic resonance venography (MRV) revealed thrombosis of the superior sagittal sinus, left transverse sinus, part of the sigmoid sinus, and small cortical veins. The patient was treated with intravenous immunoglobulin (IVIG; 0.8 mg/kg), subcutaneous enoxaparin (100 IU/kg), and acetazolamide for increased intracranial pressure, as fundoscopy revealed bilateral papilledema. Platelets normalized on the fourth day of hospitalization. Thrombophilia testing showed heterozygosity for FV Leiden and methylenetetrahydrofolate reductase C677T, while positive anticardiolipin antibodies (ACA) immunoglobulin M (30 IgM phospholipid (MPL) units) were compatible with low-risk APS. Subsequently, enoxaparin was gradually transitioned to oral warfarin. At 1-month follow-up, brain imaging revealed improvement of thrombosis and reperfusion, and papilledema was resolved, leading to cessation of acetazolamide. At 1-year follow-up, the patient remained free of relapses and discontinued anticoagulation, although she had developed episodic migraine without aura (positive family history in both parents).

2.2 | Case 2

A previously healthy 4-year-old girl residing in a town in Central Greece was admitted to the intensive care unit in June 2023 with extensive CVST. Thirteen days prior, a febrile upper respiratory tract infection was reported, and 5 days prior, she complained of drowsiness and vomiting. Thrombocytopenia (23×10^9/L, nadir level) and progressive deterioration of consciousness level were observed. Brain computed tomography revealed extended CVST, while brain MRI-MRV revealed thrombosis of the right jugular vein, the superior sagittal sinus, the right sigmoid sinus, and the right transverse sinus, with cerebral edema. Laboratory tests revealed fibrinogen of 80 mg/dL (nadir level) and elevated D-dimer (>35.5 μg/mL, highest level; Innovance) with negative inflammatory markers, while INR was 1.1 (highest level, 1.1). The child was treated with NaCl 3% and mannitol for the edema, IVIG (2 g/kg), and methylprednisolone (2 mg/kg). She was transfused twice with platelets and commenced on subcutaneous enoxaparin (100 IU/kg) and levetiracetam. Drowsiness, irritability, and reduced abduction of the right eye gradually receded. Multiplex polymerase chain reaction in nasopharyngeal sample revealed adenovirus and rhinovirus/enterovirus. Furthermore, anti–SARS-CoV-2 IgG was increased (2656 AU/mL), indicative of recent infection. Thrombophilia testing showed heterozygosity for FV Leiden, homozygosity for methylenetetrahydrofolate reductase, and positive ACA

TABLE Summary of the demographics, clinical features, laboratory findings, neuroimaging findings, and treatment of the cases.

Parameters	Case 1	Case 2	Case 3
Age (y)/sex	8/F	4/F	5/F
Past medical history	No	No	No
Family history	Systematic erythematous lupus (mother) and migraine (both parents)	Hypothyroidism (mother)	No
Initial symptoms	Headache and vomiting	Vomiting and drowsiness	Headache, nausea, and sinus bradycardia
Platelet count on admission (NR, 150 × 10^9/L to 450 × 10^9/L)	50 × 10^9/L	23 × 10^9/L	32 × 10^9/L
CRP on admission (NR, 1-10 mg/L)	12.4	24	31
Fibrinogen (NR, 200%-400%)	88	80	261
FVII (NR, 60%-120%)	49	56	N/A
INR	1.1	1.1	1.1
D-dimer (NR, <0.5 μg/mL)	>36	>35.5	27.98
AT III (NR, 80%-120%)	111	110.6	98.9
Protein C (NR, 60%-140%)	78	103.3	66.5
Protein S (%)	110	111	95
SARS-CoV-2 IgG (NR, <50 AU/mL)	328	2656.6	96.6
Respiratory panel/multiplex PCR	Adenovirus	Rhinovirus-enterovirus-adenovirus	Negative
Other infection	None	None	Streptococcal pharyngotonsillitis
FV Leiden	Heterozygosity	Heterozygosity	Negative
FII (G20210A0)	Negative	Negative	Negative
MTHFR (C677T)	Heterozygosity	Homozygosity	Negative
Brain CT or lower extremity US	No findings	Extensive CVST	CVST (left transverse sinus thrombosis)
Brain MRI/MRA/MRV	Superior sagittal, left transverse sinus, part of the sigmoid sinus, and small cortical vein thrombosis	Right jugular vein, superior sagittal sinus, right sigmoid sinus, and right transverse sinus thrombosis with cerebral edema	Left transverse and sigmoid sinus, part of external jugular vein thrombosis
Low-molecular-weight heparin	Yes	Yes	Yes
Steroids	No	Yes	Yes
i.v. immunoglobulin	Yes	Yes	Yes
Platelet transfusions	No	Yes	Yes
ENA test	Negative	Negative	Negative
ACA IgM/IgG (NR, <12.5 MPL units/<20 GPL units)	30/12	13/10	6/13
B2GPI IgM/IgG (NR, <20 units)	3/5	14/7	5/7

(Continues)

TABLE (Continued)

Parameters	Case 1	Case 2	Case 3
LA	Negative	Negative	Positive
anti-PF4/polyanion complexes IgG (LFI)	N/A	Positive	Positive
anti-PF4/polyanion complexes IgG (CLIA)	N/A	Negative	Negative

ACA, anticardiolipin antibodies; AT III, antithrombin III; B2GPI, beta-2-glycoprotein I; CLIA, chemiluminescence immunoassay; CRP, C-reactive protein; CT, computed tomography; CVST, cerebral sinus venous thrombosis; ENA, extractable nuclear antigen; F, female; FII, factor II; FVII, factor VII; FV Leiden, factor V Leiden; GPL, IgG phospholipid; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; i.v., intravenous; LA, lupus anticoagulant; LFI, lateral-flow immunoassay; MTHFR, methylenetetrahydrofolate reductase; MPL, IgM phospholipid; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; N/A, not applicable; NR, normal range; PCR, polymerase chain reaction; PF4, platelet factor 4; US, ultrasound.

immunoglobulin M antibodies (13 MPL units). Finally, we found positive anti-PF4/polyanion complexes IgG by PF4/polyanion lateral-flow immunoassay (LFI; Stago STic Expert HIT Kit, Diagnostica Stago), but negative by chemiluminescence immunoassay (CLIA) (HemosIL AcuStar Hit-IgG, Instrumentation Laboratory). On the ninth day of hospitalization, MRI revealed resolution of brain edema. At discharge, treatment included enoxaparin and brivaracetam. At 1-year follow-up, the patient is free of symptoms and signs with no relapses.

2.3 | Case 3

A 5-year-old girl residing in Athens was admitted in July 2023 due to headache, nausea, pallor, and fatigue. She was on the sixth day of treatment with amoxicillin due to fever and positive strep test result (streptococcal pharyngotonsillitis). On admission, she was ambulatory, with normal neurologic assessment. She presented bradycardia (45 bpm) without elevated intracranial pressure. Laboratory examination revealed thrombocytopenia (32×10^9/L, nadir level), fibrinogen of 261 mg/dL (nadir level), and elevated D-dimer (27.98 μg/mL, highest level; Innovance), while INR was 1.1 (highest level, 1.4). Brain MRI-MRV showed thrombosis of the left transverse, sigmoid sinus, and external jugular vein. Thrombophilia screening was unremarkable. However, elevated lupus anticoagulant 1/lupus anticoagulant 2 ratio was found (1.46; normal, 1.04-1.29) with negative ACA and beta-2-glycoprotein I antibodies. The patient had positive anti–SARS-CoV-2 IgG (96.6 AU/mL), with history of close contact 2 months ago but no documented infection. She was treated with 2 doses of IVIG (each 0.8 g/kg), 2 platelet transfusions, subcutaneous enoxaparin (100 IU/kg), and 3 pulses of methylprednisolone (30 mg/kg). Finally, she was found to have positive anti-PF4/polyanion complexes IgG by PF4/polyanion LFI (Stago STic Expert HIT Kit) but negative by chemiluminescence immunoassay (HemosIL AcuStar Hit-IgG), and enoxaparin was changed to fondaparinux. The patient showed immediate clinical response; she continued to be on treatment with enoxaparin, asymptomatic, with resolution of thrombosis. At 1-year follow-up, she remained free of relapses and discontinued anticoagulation.

3 | DISCUSSION

We present a cluster of 3 pediatric cases with postinfectious (streptococcal or adenoviral) thrombosis accompanied by thrombocytopenia, diagnosed in Athens, Greece, during a 3-month period. Infection is an independent risk factor for thromboembolic diseases, including deep vein thrombosis and CVST, even for children [8,9]. Although COVID-19–related thrombosis is rare in children, the COVID-19 pandemic highlighted the role of infections in thrombosis [3]. A recent meta-analysis found no association between the high prevalence of positive antiphospholipid antibodies in severe COVID-19 and disease outcomes, including thrombosis [10], which is also supported by other studies [11]. However, all our cases had findings indicative of low-risk APS and positive anti–SARS-CoV-2 IgG, with history of recent infection or close contact, indicating that COVID-19 may be another cause activating thromboinflammation and endothelial dysfunction.

Testing for PF4 antibodies was performed in 2 of our cases, revealing a positive result. This finding, in association with thrombosis and thrombocytopenia, raised the suspicion of the VITT-like syndrome diagnosis. VITT-like syndrome describes thrombotic thrombocytopenia resembling VITT but arising independently of recent vaccination. It is one of the anti-PF4 disorders that also include HIT and VITT.

HIT is an immune-mediated complication triggered by unfractionated or low-molecular-weight heparin administration. It arises from the formation of antibodies directed against PF4-heparin complexes, leading to platelet activation, aggregation, and subsequent thrombocytopenia [12]. These antibodies bind to PF4-heparin complexes and activate platelets via FcγRIIa receptors, culminating in a hypercoagulable state, particularly venous thromboembolism [12]. VITT shares pathophysiological features with HIT but occurs following the adenoviral vector-based COVID-19 vaccines [6]. Moreover, VITT antibodies bind directly to PF4, independently of heparin, by attaching to the heparin-binding region of PF4 [6]. This results in platelet activation and aggregation, thromboinflammation, and subsequent thrombotic events, particularly CVST [13].

The exact incidence of VITT-like syndrome are not well-established, as it is a relatively rare condition and may be underreported or misdiagnosed [6,14,15]. Clinically, VITT-like syndrome has

an acute presentation, including thrombosis in unusual sites, such as CVST, thrombocytopenia, and rarely bleeding manifestations [6,15]. Treatment includes both anticoagulation and inhibition of FcγRIIa-mediated platelet activation by high-dose IVIG [15]. Platelet transfusions are contraindicated when VITT-like thrombosis is suspected [15]. However, 3 of our patients received platelet transfusions with favorable outcome. To date, there are limited cases of VITT-like syndrome associated with adenoviral infections, but it still remains unclear if other viruses or bacteria with negatively charged polysaccharides on their surface (such as streptococcus) play key role in the pathogenesis of anti-PF4 antibodies [15].

Only a few recent reports have presented the differences in the structural characteristics and the appropriate detection tests. To our knowledge, there are limited data about VITT-like disorders in the pediatric population, restricted to only 3 patients described in 3 separate reports [6,16,17]. In our cases, 2 patients were tested and found positive for anti-PF4/polyanion complexes IgG by PF4/polyanion LFI, but anti-PF4 IgG when complexed to heparin was found negative by fully automated chemiluminescence immunoassay. The detection of VITT/VITT-like antibodies is challenging as they are not detected by HIT rapid assays or functional HIT tests. The recently developed rapid chemiluminescence assay recognizes VITT antibodies but not most of the HIT ones [18].

Although the LFI+/CLIA− profile is strongly supported by VITT-like antibodies, clear documentation of VITT antibodies would require studies such as (a) PF4-dependent platelet activation assays (PF4-enhanced serotonin-release assay), (b) specialized immunoassay ("fluid-phase ELISA"), and (c) epitope mapping of antibody binding sites on PF4 [6]. It was recently demonstrated that classic (vaccine-induced) VITT and the adenovirus-associated VITT-like disorder are essentially identical disorders on immunologic grounds [19]. However, all the above assays are not widely available in diagnostic laboratories, and globally, very few laboratories perform platelet activation assays [20].

Our positive results in the PF4/polyanion LFI are unexpected, given that adenovirus infection is believed to occasionally trigger VITT-like (not HIT-like) antibodies, and current thinking is that classic (vaccine-induced) VITT antibodies usually test negative in this rapid immunoassay (eg, 20/23 VITT sera tested negative by LFI in 1 study) [20]. Given that adenovirus-associated VITT-like disorder is believed to be immunologically identical to classic VITT [19], this suggests that possible subsequent changes in LFI assay manufacturing or other unknown factors may account for our patients' sera yielding positive LFI results. In any event, clinicians should be aware that not all laboratory assays marketed for HIT diagnosis are capable of detecting VITT/VITT-like antibodies [5].

In conclusion, this cluster of children with thrombosis and thrombocytopenia during a 3-month period may indicate a post-infectious (adenoviral or streptococcal) VITT-like disorder and provide new insights into the early diagnosis and prompt management of this disease in the pediatric population. We acknowledge the limitation of the anti-PF4 antibodies' nonproper testing; however, the positive IgG antibodies against PF4/polyanion complexes in 2 of our patients and the common clinical and laboratory characteristics in all cases show strong evidence that VITT-like disorders could be the cause of these patients. Further research with larger cohort studies is needed to describe the cause and the exact pathophysiology of such cases, as well as to determine a possible correlation with COVID-19 and an increase in their incidence during and after the pandemic.

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AUTHOR CONTRIBUTIONS

Conceptualization: H.P., V.S., D.D.; Investigation: D.D., L.M., C.K., P.K., M.B., T.B., F.T., A.D., A.Michalopoulou, I.G.S., IA.; Writing—Draft preparation: D.D., L.M., C.K., P.K., M.B., T.B., F.T.; Writing—Review and Editing: H.P., V.S., D.D., L.M., A.D., A.Michalopoulou., I.G.S., IA., A.Messaritaki.; Administration: H.P., V.S.; Supervision: H.P., V.S., D.D. All authors have read and approved the published version of the manuscript.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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