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THROMBOSIS

CASE REPORT: CLINICAL CASE

Recurrent Stent Thrombosis Following Myocardial Infarction Associated With VITT-Like Antibodies

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ABSTRACT

Early stent thrombosis is a rare complication of percutaneous intervention and is associated with significant 30-day mortality. We present a novel case of multiple recurrent early stent thrombosis consistent with spontaneous vaccine-induced thrombotic thrombocytopenia. We were successfully able to manage this unusual condition through an interdisciplinary collaboration. (J Am Coll Cardiol Case Rep 2024;29:102234) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 40-year-old man presented to the hospital with acute onset, severe left-sided chest pressure, which awoke him from sleep, that radiated to his left arm. The discomfort was associated with dyspnea and diaphoresis. One week prior, his daughter had developed upper respiratory tract infection symptoms, and the patient had developed a cough for 1 day followed by a headache that persisted until presentation. On the day prior to presentation, he received the quadrivalent influenza vaccine.

LEARNING OBJECTIVES

- To understand the role of SpVITT in the development of stent thrombosis and myocardial infarction.
- To be able to make a diagnosis of SpVITT using serum biomarkers and unique platelet-activating antibodies.

MEDICAL HISTORY

The patient has a history of obesity (body mass index: 34.1 kg/m^2) and hypertriglyceridemia.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for acute onset chest pain with dyspnea and diaphoresis includes acute coronary syndrome, aortic dissection, pulmonary embolism, and pneumothorax.

INVESTIGATIONS

A chest computed tomography scan with intravenous (IV) contrast was performed and was negative for pulmonary embolism, dissection, or pneumothorax. A 12-lead electrocardiograph (ECG) demonstrated

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ABBREVIATIONS AND ACRONYMS

ECG = electrocardiograph

FEU = fibrinogen equivalent unit

IABP = intra-aortic balloon pump

IV = intravenous

IVIG = intravenous immunoglobulin

LAD = left anterior descending coronary artery

LV = left ventricular

PF4 Ab = platelet factor 4 antibody

SpVITT = spontaneous vaccine-induced immune thrombotic thrombocytopenia

VITT = vaccine-induced immune thrombotic thrombocytopenia

nonspecific inferior lead ST-segment changes. Laboratory work-up was notable for thrombocytopenia (114,000; baseline 295,000 4 months prior) and elevated troponin-I (1,613 > 1,870 > 3,751; normal < 86 pg/mL). A D-dimer level set 18 hours after admission was 3.56 μg/mL fibrinogen equivalent units (FEUs).

MANAGEMENT

Heparin infusion was initiated for non-ST-segment myocardial infarction. Cardiac catheterization identified an 80% proximal left anterior descending coronary artery (LAD) thrombotic lesion with successful revascularization using a drug-eluting stent (everolimus-eluting stent, Abbott Vascular); therapeutic activated clotting time (>250 seconds) was maintained during the procedure (Figure 1A). Due to significant residual thrombus, the patient underwent rheolytic thrombectomy (Angiojet Thrombectomy System, Boston Scientific) and administration of a tirofiban bolus, followed by a 6-hour infusion. The stent appeared well-expanded postprocedure with mildly reduced apical LAD flow (Figure 1B). Dual-antiplatelet therapy with aspirin and ticagrelor was initiated.

Following 6-hour tirofiban infusion, the patient developed severe mid-sternal chest pain with diaphoresis and dyspnea. ECG demonstrated anterior ST-segment elevation. Emergent catheterization found multiple filling defects throughout his proximal LAD stent and native vessel distal to stent (Figure 1C) with slow apical LAD flow. Intravascular ultrasound demonstrated adequate stent expansion with mural thrombus lining the entire surface of stent including distal nonstented portion (Figure 1C). Aspiration thrombectomy of the stent and native vessel was performed, followed by LAD stent placement distal to previous stent. IV heparin and tirofiban bolus/infusion were administered followed by reloading of ticagrelor.

On completing the 6-hour tirofiban infusion, the patient developed recurrent chest pain with anterior ST-segment elevation on ECG. Catheterization demonstrated severely narrowed LAD stent with angiographic suggestion of mural thrombus within previously placed stents and occluded mid-to-distal LAD (Figure 1D). IV heparin and tirofiban bolus/infusion were administered. After multiple thrombectomy attempts, the proximal-to-mid LAD stents appeared patent, but apical LAD had TIMI flow grade 0, likely from proximal thrombus embolization. Due to ongoing chest pressure and suboptimal distal LAD flow, an intra-aortic balloon pump (IABP) was placed with initiation of continuous heparin and 18-hour tirofiban infusions.

Hematology was consulted and, despite the lack of heparin-exposure prior to the development of thrombocytopenia, recommended sending platelet factor 4 antibody (PF4 Ab) to rule out spontaneous heparin-induced thrombocytopenia. PF4 Ab was positive with an optical density of 2.75 IU (Table 1); heparin was discontinued and argatroban was initiated. A serotonin release assay was sent and subsequently found to be negative.

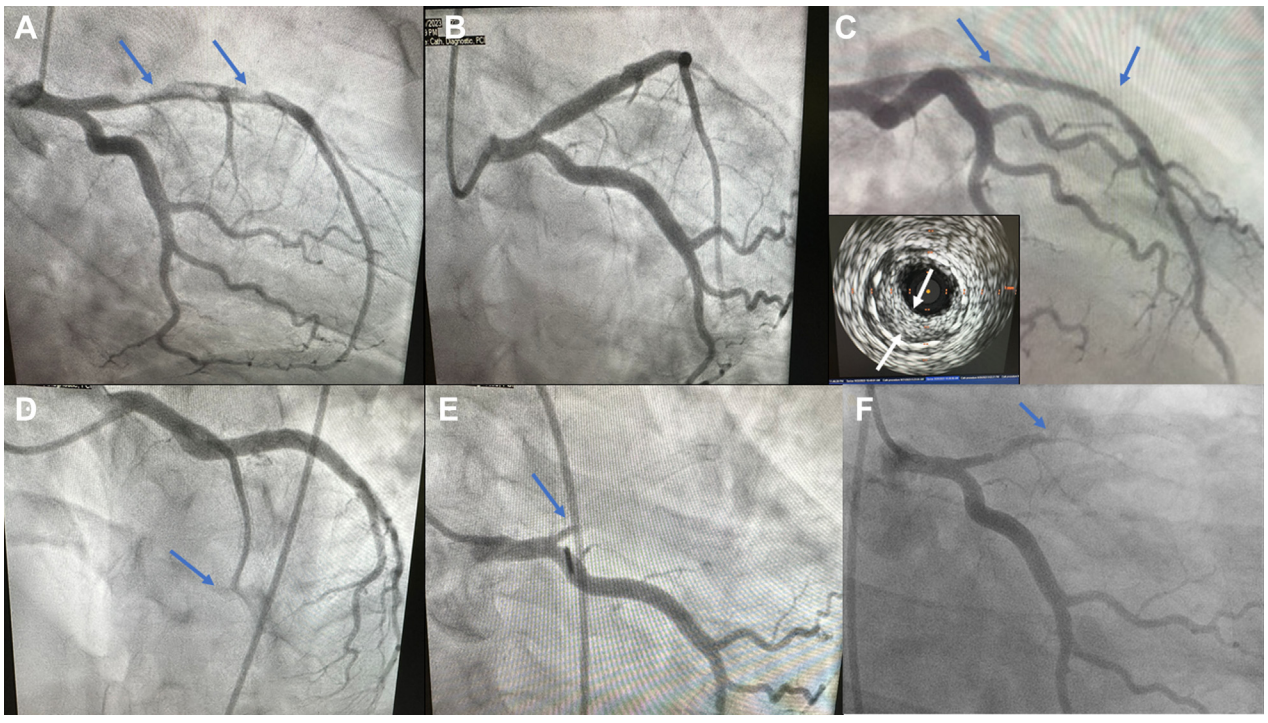
Within an hour of completing tirofiban infusion and starting argatroban, the patient developed severe chest pain with anterolateral ST-segment elevations on ECG. Repeat catheterization demonstrated proximal LAD occlusion with partially successful thrombectomy and balloon angioplasty followed by 10 mg intracoronary alteplase (Figure 1E). Argatroban was switched to bivalirudin, and tirofiban bolus/infusion was administered. At this time, the patient was transferred to our tertiary care center.

At our medical center, echocardiogram demonstrated moderate to severely reduced left ventricular (LV) systolic function (ejection fraction: 25%-30%) with LV thrombus (1.6 × 2.8 cm). He was switched from tirofiban to eptifibatide and continued on dual-antiplatelet therapy and bivalirudin. Warfarin was initiated. IABP was weaned from 1:1 to 1:2 to 1:3 over several hours without symptomatic or hemodynamic change. After 72 hours and successful weaning of IABP, eptifibatide and bivalirudin were discontinued and IABP was removed 3 hours later.

Patient remained asymptomatic for 1.5 hours following IABP removal, then developed severe chest pain and dyspnea refractory to nitroglycerin infusion with anterolateral ST-segment elevations on ECG (Figure 2B). Emergent catheterization demonstrated proximal LAD occlusion at origin of LAD stent. Partially successful rheolytic thrombectomy and angioplasty were performed with administration of intracoronary eptifibatide, but thrombus burden persisted in the mid-to-distal LAD. Following catheterization, bivalirudin and eptifibatide infusions were resumed, and warfarin was continued. A hypercoagulable evaluation laboratory panel was sent (Table 1).

Hematology was consulted and raised concern for spontaneous vaccine-induced immune thrombotic thrombocytopenia (SpVITT) given that patient had:

FIGURE 1 CA and STs



(A) Initial coronary angiography (CA) (right anterior oblique [RAO caudal] view) showing thrombotic (arrows) proximal and mid left anterior descending coronary artery (LAD) lesion. (B) Final CA (anteroposterior caudal view) with appropriate stent expansion without dissection. (C) Day 0 CA (RAO cranial view) shows stent thrombosis (ST) with multiple thrombotic filling defects (arrow). Intravascular ultrasound confirms well-apposed stent lined with mural thrombus (white arrows). (D) Day 1 CA (left anterior oblique cranial view) with recurrent ST; diffusely narrowed stent lumen, abrupt mid-distal LAD cutoff at diagonal branch (arrow). (E) Day 3 CA (anteroposterior caudal view) shows recurrent ST with abrupt cutoff at LAD stent origin (arrow). (F) Day 6 CA (RAO caudal view) shows recurrent ST of LAD stent origin (arrow).

1) an unusually aggressive series of arterial thromboses; 2) thrombocytopenia on presentation before administration of heparin; 3) an elevated PF4 Ab (optical density: 2.75) with negative serotonin release assay; and 4) an elevated D-dimer level.

The patient was treated with 2 doses of IV immunoglobulin (IVIG) for suspected SpVITT. Following IVIG administration, the patient's platelet count increased from 254,000 to 456,000 over 3 days. A repeat PF4 enzyme-linked immunoadsorbent assay had a titer of 2.91 (Zymutest HIA Elisa, Hyphen Biomed). Hypercoagulability evaluation showed no evidence of inherited or acquired hypercoagulable syndrome. Once the patient's international normalized ratio level reached 3.9, the eptifibatide infusion was discontinued followed by discontinuation of the bivalirudin 24 hours later. The patient remained asymptomatic over the subsequent days and was successfully discharged home on aspirin, ticagrelor, and warfarin. Echocardiogram on discharge demonstrated improved LV systolic function (ejection fraction: 35%) and resolving LV thrombus (1.6 × 0.4 cm).

DISCUSSION

In February 2021, a rare prothrombotic syndrome was reported in individuals who received the adenoviral vector-based COVID-19 vaccines, ChAdOx1 CoV-19 (AstraZeneca) and Ad26.COV2.S (Janssen; Johnson & Johnson).[1,2] This syndrome has been designated VITT. More recently, a similar syndrome has been reported in patients without recent exposure to the vaccine after adenovirus infection or monoclonal gammopathy of unknown significance, referred to as SpVITT.[3,4] Arterial thrombi (most often strokes) are commonly seen in these cases. There are no published cases of SpVITT or VITT associated with myocardial infarction or stent thrombosis.

TABLE 1 Relevant Laboratories and Hospitalization Events

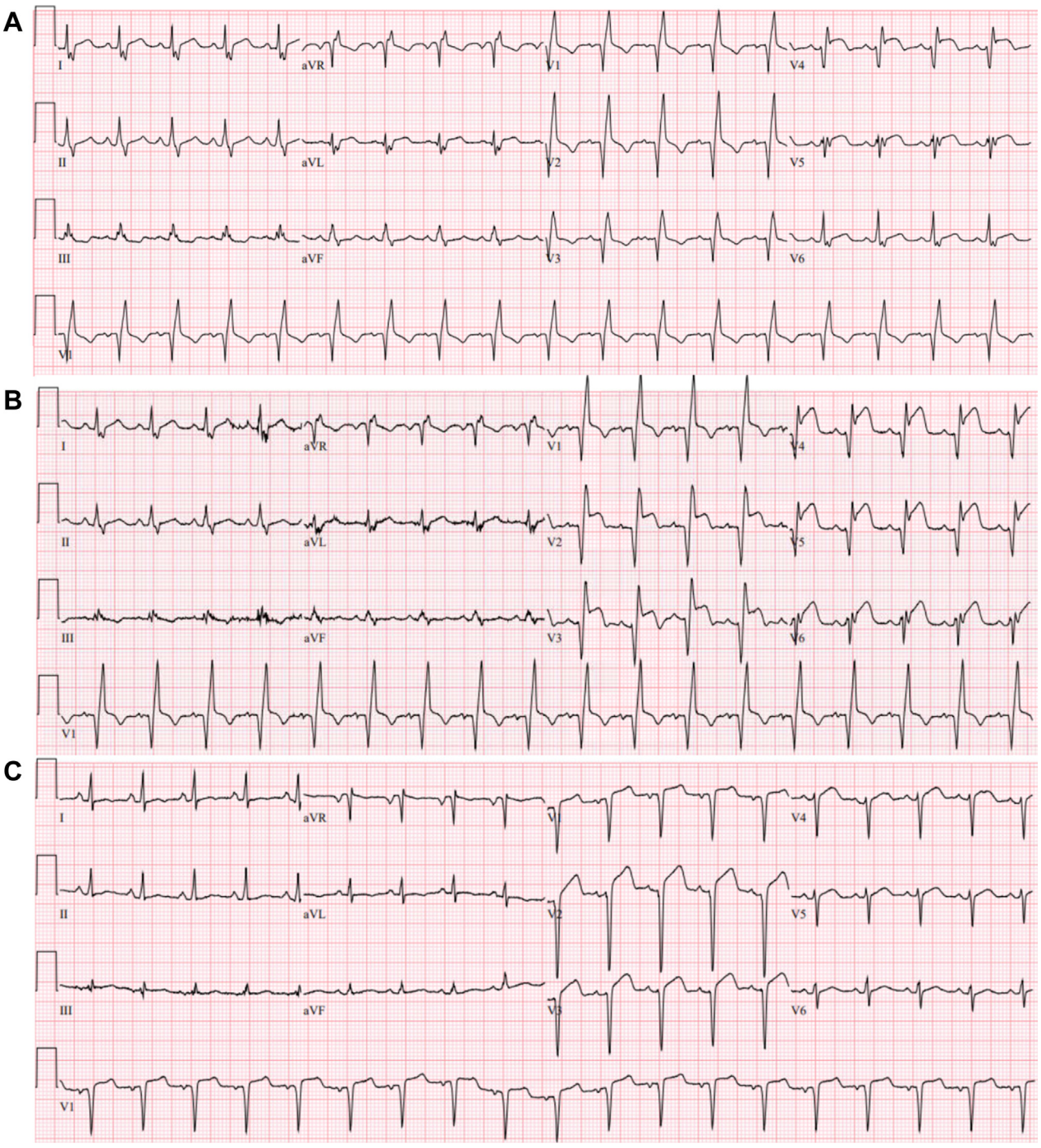
Event	Initial PCI and First ST	Second ST		Third ST	Fourth ST and IVIG Administration			
Hospital course	Day 0	Day 1	Day 2	Day 3	Day 6	Day 9	Day 10	Day 11
Troponin I, pg/mL (nl < 86)	**1,613**	**3,205**	**91,812**	**30,069**	**8,570**	**3,800**	**2,770**	**2,760**
Platelets (10^3 per μL)	**114**	**142**	**144**	152	254	456	514	514
D-dimer, μg/mL FEU (nl < 0.51)		**3.56**						
PF4 Ab optical density (nl < 0.5)		**2.75**				**2.92**	**2.78**	**2.72**
Serotonin release assay activity, % (UFH 0.1 IU/mL, 0.5 IU/mL, 100 IU/mL)			0					
Fibrinogen, mg/dL (nl 200-400)			389					
Anticardiolipin IgG				Negative	Negative			
Anticardiolipin IgM				Negative	Positive			
Anticardiolipin IgA				Negative	Negative			
Beta 2 glycoprotein IgM					Negative			
Beta 2 glycoprotein IgG					Negative			
Beta 2 glycoprotein IgA					Negative			
Lupus anticoagulant					Negative			
Antinuclear antibodies (ANA IgG)				Negative	Negative			
Neutrophil cytoplasmic antibodies					Negative			
Proteinase 3 antibody					Negative			
Myeloperoxidase antibody					Negative			
Factor V Leiden gene mutation PCR					Negative			
Factor II (prothrombin) gene mutation PCR					Negative			
Antithrombin III level, % (nl 75-135)					116			
Protein C, % (nl 83-168)					195			
Protein S, % (nl 84-134)					218			
Complement C3, mg/dL (nl 88-165)					170			
Complement C4, mg/dL (nl 14-44)					32			
Erythrocyte sedimentation rate, mm/h (nl 0-15)					68			
C-reactive protein, mg/dL (nl < 1.0)					**6.1**			

FEU = fibrinogen equivalent unit; IVIG = intravenous immunoglobulin; nl = normal; PCI = percutaneous coronary intervention; PCR = polymerase chain reaction; PF4 Ab = platelet factor 4 antibody; ST = stent thrombosis; UFH = unfractionated heparin.

Recently published work has shed light on the mechanism involved in this syndrome. Similar to heparin-induced thrombocytopenia, the presence of antibodies against PF4 with platelet-activating properties have been demonstrated; however, in VITT and SpVITT, these antibodies bind PF4 in the absence of heparin exposure.[5] VITT has been associated with development of venous and/or arterial thrombi between 4 and 42 days of vaccination.[6] The 5 criteria for "definitive VITT" include: 1) COVID vaccine 4-42 days prior to symptom onset; 2) any venous or arterial thrombosis; 3) thrombocytopenia (platelet count $<150 \times 10^9$/L); 4) positive PF4 Ab enzyme-linked immunoadsorbent assay; and 5) markedly elevated D-dimer (>4,000 FEU or equivalent). SpVITT appears to have an identical presentation with the exception of vaccine exposure. Our patient had symptoms consistent with a viral infection approximately 1 week prior to his presentation, which might well have served as the inciting event. The influenza vaccine that he received might have exacerbated the development of SpVITT through its proinflammatory effects, but we do not think the time course of its delivery nor of previous COVID-19 vaccinations (Table 2) is consistent with these being the primary cause of his prothrombotic course.

Our patient has both clinical and laboratory criteria that support a diagnosis of SpVITT (thrombocytopenia associated with a strongly positive anti-PF4 enzyme-linked immunoadsorbent assay, negative serotonin release assay, multiple arterial thrombi, and very high D-dimer level). A limitation of our study is that we did not definitely establish presence of VITT-like antibodies (unfortunately, no residual patient serum/plasma was available for referral to a specialty anti-PF4 laboratory). However, the clinical course following his IVIG treatment (including rebound in platelet count) is highly suggestive of SpVITT as the correct diagnosis.

FIGURE 2 **ECGs at Presentation, Following IABP Removal, and at Discharge**



(A) Electrocardiogram (ECG) on presentation to our medical center with sinus tachycardia, right bundle branch block, and anteroseptal infarct. (B) ECG following intra-aortic balloon pump (IABP) removal with anterolateral ST-segment elevations. (C) Discharge ECG with sinus tachycardia, anteroseptal infarct, and persistent ST-segment elevations in leads V_1-V_3.

TABLE 2 Vaccination Record

Vaccine Type	Date Received	Manufacturer
Influenza	September 19, 2023	Sanofi
Influenza	October 17, 2022	Sanofi
Influenza	September 14, 2018	Sanofi
Influenza	September 28, 2015	Sanofi
COVID-19	July 8, 2022	Pfizer
COVID-19	December 18, 2021	Moderna
COVID-19	March 16, 2021	Pfizer
COVID-19	February 23, 2021	Pfizer

For patients who fulfill criteria for VITT or SpVITT, an expedited infusion of IVIG is recommended (1 g/kg daily for 2 consecutive days) to mitigate the prothrombotic state and thrombocytopenia by preventing FcγRIIa-mediated platelet activation.[7] In addition, therapeutic anticoagulation with non-heparin-based agents should be given. In severe thrombocytopenia or life-threatening hemorrhage, plasma exchange may be considered to remove pathologic antibodies. Our patient was treated with 2 doses of IVIG with improvement in his platelet counts and no recurrent thrombi despite weaning of IV anticoagulation.

FOLLOW-UP

Three months after initial presentation, the patient has had no new episodes of thrombosis or cardiac event under guideline-directed medical therapy. He is actively participating in cardiac rehabilitation with minimal exertional symptoms.

CONCLUSIONS

This case challenges our traditional understanding of stent thrombosis etiology and should raise awareness among clinicians that this unique cause of hypercoagulability should be entertained, especially when recurrent thrombosis cannot otherwise be explained. Our case strongly suggests the diagnosis of SpVITT and reinforces the need for a better understanding of the causes of this rare (but life-threatening) condition.

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