

Received: 2019.01.05
Accepted: 2019.03.09
Published: 2019.05.28

Missed Heparin-Induced Thrombocytopenia (HIT) Diagnosis in a Patient with Acute Stent Thrombosis

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Conflict of interest: None declared

Patient: Male, 74
Final Diagnosis: Heparin-induced thrombocytopenia (HIT)
Symptoms: Chest discomfort
Medication: Heparin
Clinical Procedure: Angioplasty and bypass surgery
Specialty: Cardiology



Objective: Adverse events of drug therapy
Background: Heparin-induced thrombocytopenia (HIT) is a serious complication of heparin therapy, characterized by thrombocytopenia and high risk for venous and arterial thrombosis.

Case Report: We report an unusual case of acute stent thrombosis secondary to delayed HIT. A 74-year-old man with non-ST-segment elevation myocardial infarction had a coronary angiography which revealed 2-vessel disease. A bolus of unfractionated heparin (UFH) was administered at admission and he received fondaparinux during his hospitalization. We performed elective percutaneous coronary intervention (PCI) with stents to LAD and LCx. Two hours after PCI, the patient developed acute pulmonary edema, and repeat angiography revealed an occlusive thrombus in the ostial LAD and the LCx. A turbidimetric assay for the rapid detection of plasma anti-PF4/heparin antibodies was negative. After repeated unsuccessful attempts of balloon angioplasty and continuous thrombolysis, the patient was transferred for emergency surgical revascularisation and was treated with additional UFH followed by enoxaparin. Platelets decreased gradually to 38 k/μl 7 days after surgery, at which time enoxaparin was replaced with fondaparinux. The subsequent HIT test results were positive.

Conclusions: HIT should be considered in patients with multiple recent exposures to anticoagulants, independent of the platelet count, if there are signs and symptoms of thrombosis.

MeSH Keywords: Coronary Thrombosis • Heparin • Myocardial Infarction • Thrombocytopenia

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/914988>

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Background

Stent thrombosis is a serious thrombotic complication of percutaneous coronary intervention (PCI), which is rarely due to heparin-induced thrombocytopenia (HIT) [1,2]. The incidence of HIT in patients who received unfractionated heparin (UFH) is reported to be 0.1–1%, and the incidence of thrombotic events is approximately 50% in patients confirmed with HIT [3]. HIT is an adverse immune-mediated reaction, characterized by venous and arterial thrombosis [4]. Platelet factor 4 (PF4) binds and neutralizes heparin after heparin exposure. The PF4-heparin complex leads to the formation of IgG antibodies. The 3-component antigen-antibody immune complex composed of IgG, PF4, and heparin binds to the FcγRIIIa receptors of platelets, resulting in platelet activation [5,6]. During activation, platelets release pro-inflammatory, pro-thrombotic, adhesive, and chemotactic mediators that propagate, amplify, and sustain thrombus formation [7]. Nevertheless, drug-induced thrombocytopenia has been reported with several anticoagulants and antiplatelet agents used in treatment of acute coronary syndromes or during PCI.

Case Report

A 74-year-old man was admitted with non-ST-segment elevation myocardial infarction (NSTEMI) to regional hospital 10 days before the admission to our hospital, where he received 5000 units of UFH intravenously (IV) at the Emergency Department. The day after, a coronary angiogram was performed, which revealed 2-vessel disease – severe stenoses of the ostial left anterior descending artery (LAD) and mid-circumflex artery (LCx). During hospitalization, he received fondaparinux 2.5 mg subcutaneously once daily for 5 days. Following a Heart Team discussion, the patient underwent PCI to our center, with 1 stent in the proximal LAD (Resolute 2.5×26 mm) and 2 overlapping stents in the mid-LCx and proximal LCx (Resolute 2.5×12 mm) 12 days after his first admission (Figure 1A). During the procedure, 5000 units of UFH was administered IV. Other medications included aspirin 100 mg, clopidogrel 75 mg, statin, angiotensin-converting enzyme inhibitor, and b-blocker. Five days before PCI, the platelet count was normal (300 K/μl). The final result of PCI was satisfactory, and the patient was symptom free. However, 2 h after PCI, the patient developed prolonged chest pain with new LBBB and acute pulmonary edema. Repeat angiography revealed an acute occlusive thrombus in the ostial LAD (Figure 1B). An intra-aortic balloon pump was inserted and a new PCI to LAD was attempted, after the administration of 5000 units of UFH. The LAD was crossed with a BMW guide-wire and multiple balloon inflations were performed across the LAD, restoring a Thrombolysis In Myocardial Infarction (TIMI)-3 flow. However, during the procedure, accelerated thrombosis was noted to the stented LCx and in the left main. A new BMW

was advanced in the LCx, and balloon inflations were repeated (Figure 1C). Due to accelerated thrombosis, an urgent coagulation profile was requested, which showed the activated clotting time was 240 s (normal range 90–150) and good platelet response to clopidogrel treatment, measured with light transmission aggregometry (LTA). A rapid turbidimetric assay HemosILHIT-Ab_(PF4-H) for the semi-quantitative detection of IgG-IgM-IgA antibodies in plasma was negative (performed using an ACL TOP® hemostasis analyzer; Instrumentation Laboratory, Werfen Group, Munchen, Germany).

Despite multiple dilatations with balloons, the residual coronary thrombus burden remained very high. Due to potential bleeding risk, thrombolysis was not performed. The patient's condition deteriorated, with recurrent episodes of ventricular fibrillation, so he was intubated and transferred for emergency surgical revascularisation (Figure 1D). He received 2 vein grafts to the LAD and LCx. In addition to UFH the patient had received 4 and 2 h before surgery, he was also treated with UFH intraoperatively. Thromboprophylaxis with enoxaparin (2000 anti-Xa subcutaneously twice a day) was started 24 h after surgery. The platelet count decreased gradually, from 132 k/μl 2 days after surgery to 38 k/μl 7 days after surgery. On the 7th day after surgery, due to a high probability of HIT, enoxaparin was replaced with fondaparinux (1.5 mg subcutaneously once daily) (Figure 2). A rapid immunoassay test (Asserachrom HPIA-IgG, IgA, IgM [Stago Diagnostica, France]), Asserachrom HPIA-IgG (Stago Diagnostica, France), and functional in-house HIPA (Heparin-Induced Platelet Aggregation) were positive 7 days after surgery and a serotonin test was also positive 7 days after surgery (Table 1).

An echocardiogram showed severe left ventricle dysfunction, with ejection fraction of 20% and akinesia of apical and anterolateral walls. The patient had multiple ischemic strokes and kidney failure requiring hemodialysis, and eventually died after a prolonged ICU stay (Figure 1E, 1F).

Discussion

Acute stent thrombosis is reported in up to 0.5–0.7% of cases in the first 24 h after PCI (with either drug-eluting or bare-metal stents) [8]. Several factors have been associated with early stent thrombosis, including residual target lesion thrombus or dissection, stasis, stent underexpansion, or a combination of these [9–13]. Although supportive anticoagulant agents are used in the treatment of such cases, UFA and (rarely) low-molecular-weight heparin or glycoprotein IIb/IIIa receptor blockers have been implicated in the abrupt onset of an adverse immune-mediated reaction of HIT [14,15].

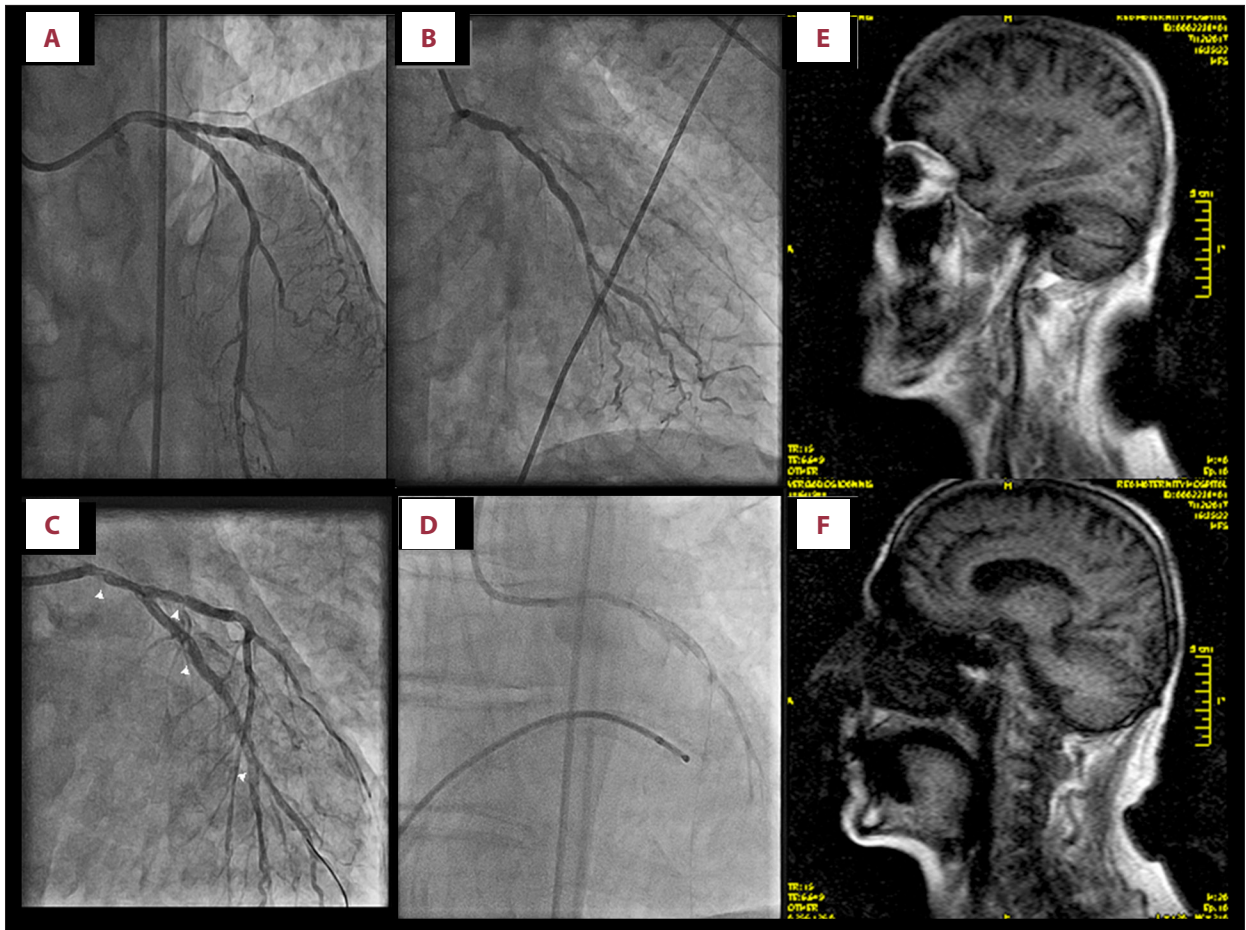


Figure 1. (A) Final angiographic result after electively stenting of left anterior descending coronary artery (LAD) and left circumflex coronary artery (LCx). (B) Acute total thrombotic occlusion of the proximal LAD. (C) Thrombus (arrows) from the left main coronary artery to the previously deployed stents at the LAD and LCx during emergency PCI. (D) Extensive thrombus in both culprit arteries with Thrombolysis In Myocardial Infarction (TIMI) flow 0–1. (E, F): Magnetic resonance imaging shows cerebral infarctions.

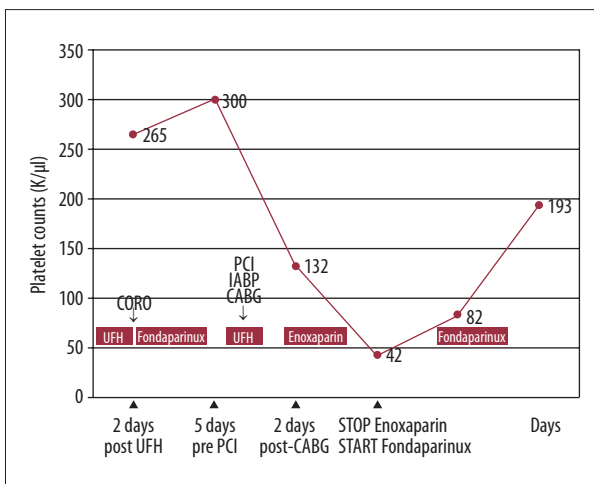


Figure 2. Clinical course and platelet count trend during hospitalization.

Table 1. Timing of positive heparin-induced thrombocytopenia (HIT) test results.

	Tests for HIT	
	Post-PCI	7 days after CABG (stop enoxaparin)
Anti-PLT (IgG) for UFH (Elisa)	Negative	Positive
Anti-PLT (IgG, IgM, IgA) for UFH		Positive
Functional test (aggregation)		Positive
Serotonin test (radiomarker)		Positive

HIT is characterized by both venous and arterial thrombotic events, with the former being much more common [16,17]. The diagnosis of HIT is based on a decrease in the platelet count by more than 50% or thrombosis [18]. The 4Ts scoring system

estimates the probability of HIT, incorporating 4 features of HIT: (1) degree of thrombocytopenia, (2) timing of platelet fall after heparin exposure, (3) the presence of thrombosis, and (4) absence of any other cause of thrombocytopenia [18]. A total score of less than 4 points has a high negative predictive value (97–100%), but the positive predictive value is highly variable (40–82%) for a total score more than 6, and it is likely dependent on the experience of the user and on the clinical setting [19]. Patients with intermediate or high 4Ts scores need additional laboratory tests.

The onset of thrombocytopenia following heparin administration varies based on the patient's prior history of exposure [20,21]. It usually occurs 5–10 days after the initial exposure to heparin, and HIT antibodies may be present for approximately 120 days after UFH [22]. A rapid decline in platelet count, often within hours, can occur in patients with recent exposure to heparin and with measurable levels of PF4-heparin antibodies. In our case, PF4-heparin complexes were assumed to be produced during coronary angiography. The subsequent treatment with fondaparinux did not allow the evolution in classical HIT according to the diagnostic criteria of this syndrome. The formation of antibodies against the heparin-PF4 complexes occurred when the bolus dose of UFH was administered prior to the elective PCI. The re-exposure to UFH during emergent PCI resulted in accelerated platelet reactivation and profound thrombosis of stented and non-stented vessels. PF4/heparin antibodies, which were already present in the plasma of the patient but in a low concentration and so non-detectable by the biological tests, reacted with UFH and triggered platelet activation. Assays for HIT antibodies are classified into: a) PF4-enzyme-linked immunoassay (ELISA) and b) platelet activation or functional assays. PF4 ELISA was urgently performed on-site and came back negative. The HIT

ELISA method has substantially variable sensitivity and specificity, with significant limitation of false-negative results, due to the presence of an antigen other than PF4 [23,24].

Treatment with enoxaparin during the post-CABG period generated platelet activation, triggering the typical manifestation of HIT (8 4T score) and, on the clinical level, cerebrovascular events. The results of the heparin-induced platelet aggregation and the serotonin release assay (SRA) were positive 7 days after CABG. They are both complex tests, which many laboratories do not perform. SRA has much greater specificity, but requires radioisotope and reactive donor platelets, as well as reagents, which are all unavailable at most clinical laboratories [25]. For most clinicians, both assays are available only as “send-out” tests and did not yield results quickly enough to inform initial clinical decision-making.

Conclusions

This case highlights an interesting challenge in the diagnosis of HIT in the setting of acute stent thrombosis. HIT should be considered in patients with multiple recent exposures to anticoagulants, independent of the platelet count, if there are signs and symptoms of thrombosis. HIT should be ruled out by antibody test and serotonin release assay, which are not always available on-site. Prompt identification and management of acute stent thrombosis with HIT is of paramount importance to avoid serious complications.

Conflict of interest

None.

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