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CASE REPORT
Coronary heart disease

Native coronary artery thrombosis in the setting of heparin-induced thrombocytopenia: a case report

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Background Heparin-induced thrombocytopenia (HIT) is a rare complication of heparin therapy. Its pathogenesis includes thrombotic events that can rarely affect the coronary arteries.

Case summary We report a 67-year-old woman who presented with extensive lower extremities deep venous thrombosis. After being treated with heparin, she developed an ST-elevation myocardial infarction secondary to an acute thrombus formation. The patient's platelets dropped within 6 days from the procedure and her heparin-PF4 IgG antibody and serotonin release assay were positive confirming the diagnosis of HIT.

Discussion Prothrombotic states, such as HIT, are associated with increased risk for coronary thrombosis and ischaemia. Heparin-induced thrombocytopenia can cause coronary complications usually in previously disrupted coronary vessels and bypass grafts. Here, we demonstrate that spontaneous thrombosis can occur in a previously untreated native coronary artery in a patient with HIT.

Keywords Case report • Coronary thrombosis • Heparin-induced thrombocytopenia • Procoagulation • Percutaneous coronary intervention • ST-elevation myocardial infarction

Learning points

- Heparin-induced thrombocytopenia (HIT) can lead to acute coronary thrombosis leading to ST-elevation myocardial infarct.
- ST-elevation myocardial infarct can be the only manifestation of HIT in critically ill patients, and high index of suspicion is required when thrombocytopenia is noted.

Introduction

Heparin induced-thrombocytopenia (HIT) is a life-threatening rare complication of heparin therapy. Its pathogenesis includes the formation of antibodies against platelets, which eventually lead to paradoxical thrombotic complications.[1–3] Venous thrombosis is far more common than arterial thrombosis in HIT, although both occur. In patients with HIT, native coronary arteries are rarely implicated by thrombus formation and this almost always occurs in the setting of venous coronary grafts or previous coronary interventions.[4–10] Here,

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we describe a case of thrombus formation in a native coronary artery causing an ST-elevation myocardial infarct (STEMI) secondary to HIT.

Timeline

Date	Event
17 December 2017	Initial presentation with bilateral lower extremities deep venous thrombosis, and heparin drip initiated
21 December 2017	Patient underwent catheter-directed thrombolysis to lower extremities
23 December 2017	Heparin drip stopped, and apixaban therapy initiated
29 December 2017	• Due to the extent of the thrombosis, she underwent repeat catheter-directed thrombolysis, with re-initiation of heparin intravenous therapy • Subsequently, she developed compartment syndrome and underwent a partial fasciotomy
1 January 2018	• Patient complained of chest pain, EKG showed ST-elevation in inferior leads, cardiac catheterization showing a thrombus of the right coronary artery done with subsequent stenting • Platelet nadir, suspicious for heparin-induced thrombocytopenia (HIT) • Heparin-induced thrombocytopenia PF4 antibody positive • Heparin drip stopped, and anticoagulation switched to apixaban
3 January 2018	Serotonin release assay came back positive confirming HIT

Case summary

The patient is a 67-year-old woman with a history of hypertension, acute kidney failure, a provoked pulmonary embolism needing an inferior vena cava (IVC) filter placement due to gastro-intestinal bleed, who presented with bilateral lower extremity swelling and pain. She is not known to have ischaemic heart disease or previous angina symptoms.

Her symptoms have been progressively worse over the past few weeks. On initial presentation to the hospital, she was haemodynamically stable with a temperature of 36.3°C, heart rate of 117 b.p.m., respiratory rate of 20/min, blood pressure of 113/55 mmHg, oxygen saturation of 100% on room air. She was alert and oriented, not in acute distress. Her lungs were clear on auscultation and her heart sounds were normal and regular. Her lower extremities were erythematous, warm, painful to touch, and presented a non-pitting oedema bilaterally. Laboratory studies were significant for a creatinine of 3.8 mg/dL from a baseline of 0.8 mg/dL (normal 0.5–1.1 mg/dL), haemoglobin of 15.4 g/dL (normal 11.0–16.0 g/dL), platelets of 204 000/μL (normal 150 000–400 000/μL), and a lactic acid of 3.4 mmol/L (normal 0.5–2.2 mmol/L). Lower extremities duplex and renal ultrasounds demonstrated extensive occlusive thrombi throughout her lower extremities veins extending proximally which may have compromised renal venous return. However, the kidneys were not enlarged. The patient's Wells score was 7.5. A nuclear lung perfusion scan was performed and showed evidence of subsegmental areas of decreased activity in both lungs, the right more than the left, suggestive of pulmonary emboli. Angiography revealed that the thrombosis is extending to IVC filter and bilateral renal veins. In this perspective, she received local thrombolysis through two ultrasound-assisted catheters-directed thrombolysis (tissue plasminogen activator at a rate of 0.5 mg/h for a total of 10 mg in combination with heparin) and was also started on systemic intravenous heparin treatment. Thereafter, she was transitioned to apixaban for anticoagulation and the heparin was stopped. Due to the extent of the thrombosis, the patient underwent a repeat local catheters-directed thrombolysis. Subsequently, her course was complicated by right lower extremity compartment syndrome, for which she underwent a partial fasciotomy and was switched to intravenous heparin treatment in the peri-operative phase. She developed a sudden onset of substernal chest pain and an electrocardiogram showed ST-elevation in leads II, III, and AVF. Subsequently, she underwent coronary angiography, which confirmed a thrombus formation in the distal portion of the right coronary artery (RCA) (*Figure 1A*; also Supplementary material video (pre stenting)). The rest of the coronary angiography showed that the left main artery had a 20% stenosis, the left anterior descending artery had 50% stenosis, and the left circumflex artery had diffuse irregularities. Thrombus aspiration was not performed, but the lesion was crossed using a Prowater wire followed by a 2.5 mm Trek balloon inflation. A drug-eluting stent was placed successfully with return of TIMI III flow in the RCA (*Figure 1B*); also Supplementary material video (post stenting)). A recent transthoracic echocardiogram was reviewed and showed an intact atrial septum without evidence of an atrial septal defect or patent foramen ovale confirmed by agitated saline study. A follow-up echocardiogram post-myocardial infarction showed hypokinesis of the mid infero-lateral segment, akinesis of the basal inferior segment. All other segments appeared to contract normally. She also was noted to have a new onset thrombocytopenia, with a platelet nadir of 109 000/μL from baseline of 271 000/μL (>50% drop from baseline) within 6 days of heparin reintroduction. Her other laboratory tests included haemoglobin of 8.3 g/dL and creatinine of 1.4 mg/dL. Calculation of the 4T score revealed a count of 7, which implied a 64% probability of having HIT. Heparin-PF4 IgG antibody (1.297 optical density, normal <0.4000) and serotonin release assay were positive, confirming the diagnosis of HIT. The decision was to treat her with apixaban 5 mg twice daily. She was discharged on triple therapy with aspirin 81 mg daily, ticagrelor 90 mg twice daily with a plan to continue on dual-antiplatelet therapy for 1 year, and apixaban for lifelong anticoagulation. The patient's platelets and kidney function were back to normal within days (*Figure 2*). The patient was seen 20 days after her discharge. She had +1 oedema in the lower extremities, without erythema or pain. She denied having angina symptoms. Her

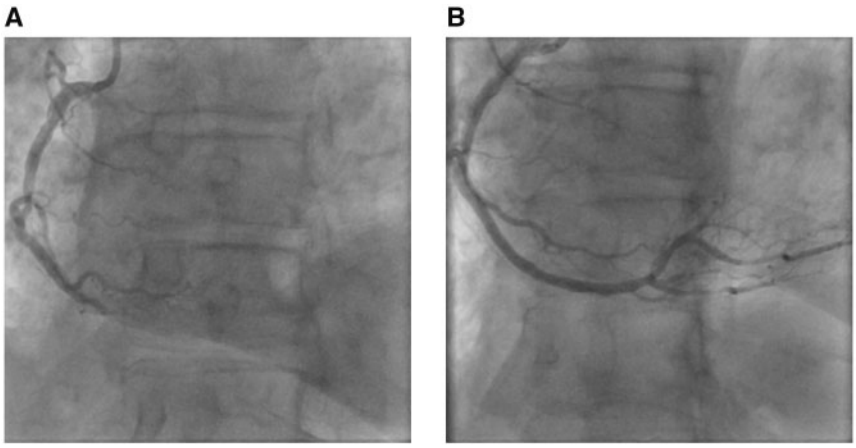

Figure 1 (*A*) Angiogram showing a total occlusion of the distal right coronary artery by a thrombus. (*B*) Post-stenting angiogram showing widely patent right coronary artery.

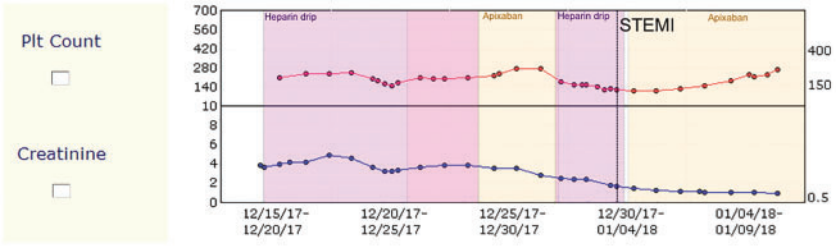

Figure 2 Platelets (red line) and creatinine (blue line) trends during the patient's course. Heparin infusion (purple background), apixaban therapy (orange background), and the onset of the right coronary artery ST-elevation myocardial infarct (black vertical dashed line).

haemoglobin was 8.0 g/dL, platelets 313 000/μL and creatinine was 1.0 mg/dL. Her electrocardiogram showed sinus rhythm with normal axis, inferior T wave nonspecific abnormalities. An echocardiogram at that time showed that the basal inferior akinesis became aneurysmal without any other significant changes.

Discussion

Heparin-induced thrombocytopenia is a well-recognized immunological phenomenon secondary to heparin exposure. It is estimated that the risk of developing HIT after exposure to unfractionated heparin to be 2.6%.[1,2] The underlying pathogenesis involves the development of antibodies against platelet factor 4 (PF4) bound to heparin, called HIT antibodies. Those immunoglobulins can bind to platelets and cause a wide-spread platelet activation leading to venous and arterial thrombosis and activation of coagulation cascades. This eventually leads to platelet consumption and thrombocytopenia. Clinically, these events tend to occur within 5–14 days of initiation of heparin, especially in the setting of previous heparin exposure. High index of suspicion with the aid of scoring systems such as '4T' score is required for the diagnosis of HIT. The pattern of thrombosis in HIT tends to be dominant on the venous side. However, arterial thromboembolic complications can occur causing, commonly, limb ischaemia.[3]

Coronary thrombosis can rarely occur in association with HIT. This can manifest in acute myocardial ischaemia and can be a life-threatening emergency when it occurs. There had been previous reported cases of HIT causing coronary thrombus formation, however most in the setting of either previous coronary intervention, stenting or in coronary bypass grafts.[4–10]

Upon review of the literature, we identified multiple case reports of HIT complicated by coronary arterial thrombosis (*Table 1*). Female-to-male ratio was 2:1. All of the cases were preceded by initiation of unfractionated heparin. The time until thrombocytopenia ranged from 1 h to 96 h, with an average of 35 h, since the initiation of heparin. The platelet nadir ranged from 4×10^9 to 109×10^9 per mL, with an average of 5×10^9 per mL. Time until coronary artery thrombosis ranged from 0 h to 96 h, with an average of 24 h, since the initiation of heparin. There was only one case of HIT that involved a native, not previously treated, coronary artery.[9]

Our case heightens the awareness of the possibility of thrombotic complications of HIT in native coronary arteries. This is important, as early recognition and treatment of coronary thrombosis with HIT requires immediate discontinuation of all heparin products and

Table 1 Case reports of HIT complicated by coronary arterial thrombosis

Age	67	79	76	62	39	72	55	63
Gender	Female	Female	Male	Female	Male	Female	Female	Male
Heparin exposed	UFH	UFH	UFH	UFH	UFH	UFH	UFH	UFH
Platelets baseline	265 000	241 000	257 000	443 000	160 000	160 000	108 000	NA
Platelets nadir	109 000	13 000	109 000	4000	49 000	28 000	90 000	67 000
Time until thrombocytopenia (h)	48	48	1	48	5	24	24	96
Time until thrombosis (h)	36	0	0	0	24	24	24	96
Alternative anticoagulation	Apixaban	None	None	Argotraban	Bivalirudin	Argotraban	Argatroban + Eptifibitide	Lepirudin
Coronary artery	RCA	Presumed LAD—with PCI	LAD->LMCA —previous PCI	RCA with stent	LAD with stent	All grafts and native coronaries thrombosed	RCA with stent	RCA
Previous interventions?	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Other thrombotic complication	None	None	None	None	None	None	Right hand cyanosis +parasthesia	None
Notes	Native	Intra-PCI complication	History of CABG	In-stent thrombosis	In-stent thrombosis	CABG few days prior	In-stent thrombosis	Native
Reference		Gupta *et al.*[5]	Ziakas *et al.*[4]	Shin *et al.*[6]	Hussain *et al.*[8]	Matsue *et al.*[10]	Gallagher *et al.*[7]	Iqbal *et al.*[9]

initiation of anticoagulation with different agents in efforts to prevent further progression.[3] The general management of the myocardial infarction itself would remain the same. This would include dual antiplatelet therapy, beta-blockers, statins and angiotensin I converting enzyme inhibitors if required. Urgent PCI is necessary for STEMI and in certain cases of Non-STEMI.[11]

An alternative form of anticoagulation in patients with HIT stops the progression of the disease and further antibody formation, and resolves further thrombosis due to platelet activation. Alternatives usually include direct thrombin inhibitors such as argotraban or bivalirudin, fondaparinux, danaparoid, or direct oral anticoagulants (DOACs) such as apixaban or rivaroxaban. The choice of anticoagulant is dependent upon factors that include the patient's renal and hepatic function, as well as the acuity of the patient's thrombotic complications.[3]

There are previous reports of using DOACs successfully in the initial management of HIT.[12] However, this experience in using DOACs in HIT is limited and is mostly using rivaroxaban. It was shown that apixaban may provide an option for an oral alternative for patients with HIT as it did not cause platelet activation.[13] Our patient received apixaban as sole alternative anticoagulation with resolution of thrombocytopenia and no progression or recurrence of thrombosis.

Conclusion

Heparin-induced thrombocytopenia-associated coronary artery thrombosis is a rare, but life-threatening, complication. Here, we present a case of a native coronary thrombus that developed in a patient with HIT causing a STEMI. This provides further proof that clinicians should be aware of this deadly complication, as early treatment is life saving. We also show that this can occur even in a previously untreated native coronary artery. Further, our case supports the successful use of apixaban as monotherapy in the treatment of HIT along with the usual management of acute coronary syndromes.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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