Arterial and Venous Thrombosis From Delayed-Onset Heparin-Induced Thrombocytopenia

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Abstract

Heparin Induced Thrombocytopenia (HIT) is a life threatening condition which is caused due to antibody formation following exposure to heparin or heparin products. It occurs due to the formation of Platelet Factor 4 antibodies (PF4). HIT is classified into 3 categories based on the duration between heparin exposure and onset of drop in platelet counts. A less common form of HIT is delayed onset HIT which occurs more than 9 days after exposure to heparin or heparin products. In this report we would like to present a rare case of delayed onset HIT which occurred in our patient who presented with rhabdomyolysis and Non ST elevation myocardial infraction (NSTEMI); which resulted in limb ischemia which needed to be treated by amputation of the affected area. We also highlight further management of patients who have thrombotic disease in the setting of HIT and review literature of how heparin or heparin products can be reintroduced in such patient who cannot be managed by other anticoagulation.

Keywords: Delayed onset HIT, HIT, Heparin induced thrombocytopenia, NSTEMI, Rhabdomyolysis

1. Background

Heparin-induced thrombocytopenia (HIT) is potentially life-threatening, warranting prompt recognition and intervention. HIT typically presents with thrombosis which is more commonly venous thrombosis, however, arterial thrombosis has been reported which is less common.[1] Three main patterns of HIT have been reported based on the interval between heparin exposure and onset of thrombosis or fall in platelet count.[2] Heparin primarily exerts its action by binding to antithrombin III. Platelet factor 4 (PF4) can bind and neutralize the anticoagulant activity of heparin, and induce generation of antibodies to the PF4-heparin complex. This can result in thrombocytopenia and thrombosis of variable effect. We report a rare case of arterial and venous thrombosis from delayed-onset HIT.

2. Case summary

A 68 year old woman was brought to the emergency department after being found unresponsive at home for an unknown period of time. She was found down, surrounded by urine and fecal material. Her medical history was significant for rheumatoid arthritis and hypertension. Given that she had persistent altered mental status warranting investigation, most of her initial history was obtained from her family, who did not live with her, hence initial history on presentation was limited.

Initial physical examination was remarkable for the patient being soiled with urine and feces, occasionally grimacing, along with stage 2 pressure ulcers on bilateral anterior thighs, skin excoriation/maceration under bilateral breasts and left lateral hip. On neurological examination she was not alert or responding, but would withdraw to painful stimuli. She moved all extremities spontaneously but had resistance to passive movements including neck flexion. Pupils were reactive bilaterally and measured 3 mm. Cardiac, pulmonary and abdominal examination did not show any significant findings.

Laboratory diagnostics revealed elevations in serial measurements of troponin-I which was 3.27 ng/mL (reference range 0.00–0.045 ng/mL), peaking at 34.7 ng/mL (reference range 0.00–0.045 ng/mL). A 12-lead electrocardiogram did not reveal any acute

ischemic changes and was significant only for sinus tachycardia. A non-contrast CT scan of the head did not reveal any acute intracranial pathology. A plain film radiograph of the chest was significant for linear atelectasis of the right upper lobe but did not show any cardiac or pulmonary pathology.

The patient was admitted to the hospital for further workup of her altered mental status. Given her unstable state, medical management for NSTEMI was initiated with aspirin, statin, beta blocker and 48 h continuous heparin infusion therapy.

Patient's mentation improved, however on the 9th day of hospitalization, patient developed left lower extremity swelling and associated severe left side toe pain. On examination the first two toes appeared erythematous and tender to touch with scattered dark areas of discoloration. She was also noticed to have a warm and tender left leg with 2+ pitting edema to the mid-calf. On vascular exam, there were no palpable or dopplerable dorsalis pedis and posterior tibial pulses on the left side. Venous duplex ultrasound revealed isolated left peroneal deep venous thrombosis (DVT). An arterial duplex study revealed left common femoral artery velocity of 200−400 cm/s, consistent with a 50%−75% stenosis (moderate occlusive disease) and inability to visualize arterial flow in left profunda, distal left popliteal, proximal left posterior tibial and left dorsalis pedis arteries (Fig. 1). CT angiogram further revealed multiple arterial emboli, including embolism to the left internal iliac artery, likely embolus to deep femoral artery, and possible embolus to the left popliteal artery with reconstitution of the tibial arteries.

The patient underwent left lower extremity angiogram via right common femoral artery access, with angioplasty to the left popliteal and posterior tibial arteries with mechanical thrombectomy − AngioJet with initiation of thrombolysis therapy. During recovery, she developed worsening pain, pulselessness, cyanosis, and poikilothermia of the left lower limb. There were no doppler signals to the left foot. She was taken to the operating room for emergent endarterectomy, where she underwent a successful left femoral cutdown with thrombectomy of left superficial femoral artery and left profunda femoral artery. At the completion of the case, there was reestablished two vessel run-off to the left lower extremity with positive strong left posterior tibial, left anterior tibial, and left peroneal doppler signals.

The patient was reinitiated on systemic anticoagulation with heparin infusion for DVT, given high risk factors present for extension into the
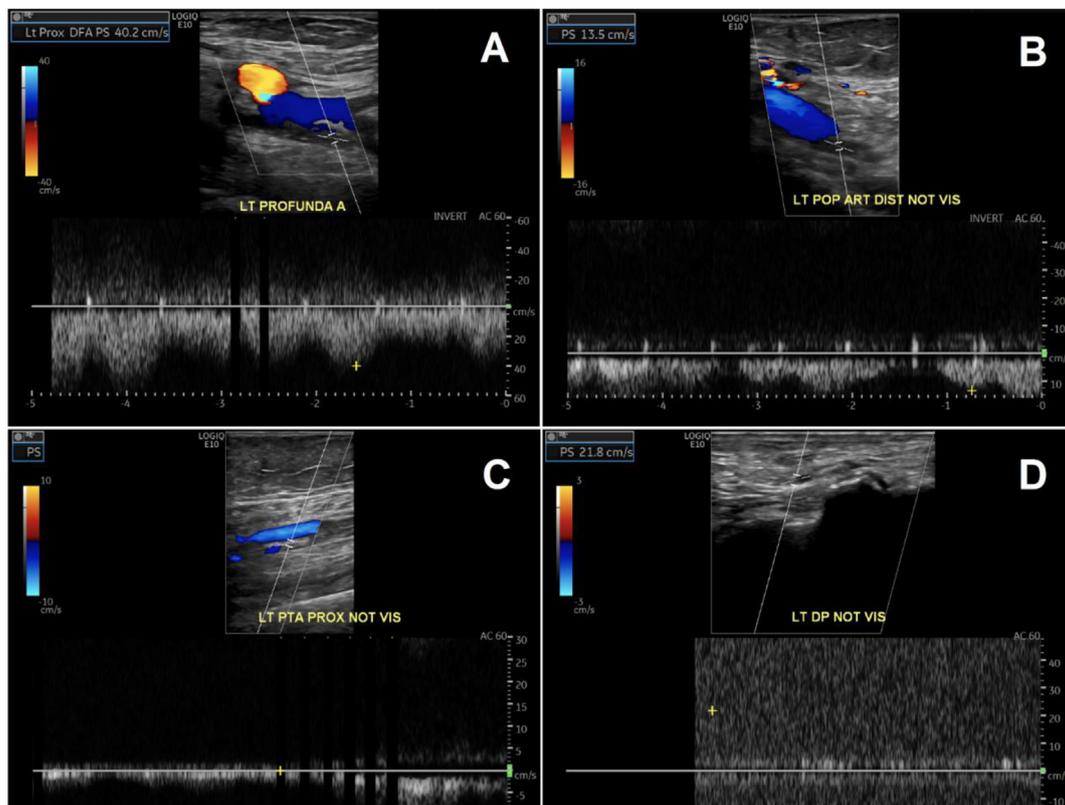

Fig. 1. Arterial duplex of left lower extremity. Arterial flow not visualized in: (A) Left profunda artery (B) Distal left popliteal artery (C) Proximal left posterior tibial artery (D) Left dorsails pedis artery.

proximal venous system and pulmonary embolism. Due to simultaneous presence of both arterial and venous thrombi, a workup for underlying causes of hypercoagulability was performed and was unrevealing. The specific values were interpreted considering the ongoing heparin therapy. Antithrombin III was 51% (reference range: 80–120%), protein C activity level 75% (reference range 63–153%), protein S activity level 175% (reference range: 63–153%). Fibrinogen was 513 mg/dL (reference range: 203–534 mg/dL), anticardiolipin antibody IgG was 10 GPL (reference range: ≤14 GPL) but IgM was elevated at 42 MPL (reference range: ≤15 MPL). Beta-2 glycoprotein antibodies were negative. Laboratory findings were also consistent with significant thrombocytopenia. The initial drop in platelet count from 423,000/uL to 174,000/uL (reference range 145,000–400,000/uL) was attributed to dilution given aggressive volume resuscitation. Around day 9 of hospitalization, platelet numbers have dropped to 100,000/uL. High suspicion for HIT was raised, based on a 4T score of 64%, and subsequently the serotonin release assay with optical density values of 1.677 (reference range: 0–0.349) confirmed the diagnosis of HIT.

Additionally, during this hospitalization she underwent a staged cardiac catheterization, 12 days after initial presentation, which revealed a thrombus in the circumflex artery, and involved the placement of a single drug-eluting stent. A transthoracic echocardiogram showed mildly reduced ejection fraction (50–55%) along with mild inferior/inferolateral wall hypokinesis and grade I diastolic dysfunction.

She was followed by the limb salvage team for her left foot (Fig. 2) and underwent transmetatarsal amputation. Post surgery she was discharged to rehab on apixaban.

3. Discussion

The initial sign of HIT is a drop in the platelet count, with DVT being a more severe manifestation. Arterial thrombosis is less common, but can lead to significant mobility including complications like cerebrovascular accident, myocardial infarction, acute limb ischemia, peripheral artery occlusion and renal vascular occlusion. White clot syndrome refers to platelet rich aggregations leading to arterial thrombosis.[1]

HIT can present in three main patterns based on the incidence of thrombocytopenia in relation to heparin exposure.[2] The most common pattern is typical onset, which occurs within 4–10 days of initial heparin exposure, with a drop in platelet count by greater than 50%. The second pattern is delayed onset HIT which usually occurs after cessation of heparin products with the average duration being 9 days after heparin cessation; however reports suggest durations as long as 40 days after heparin cessation.[3] This can occur in approximately 13–15% of cases.[4] Early onset HIT can occur in patients who have persistent antibodies to heparin after having received it within the prior three months. The median time the platelet drop in such patients occurs within 10.5 h of initial heparin therapy.[5]

Fig. 2. Appearance of distal left lower extremity with gangrenous changes requiring trans metatarsal amputation.

There are certain risk factors associated with development of HIT including route of administration, type of product administered (unfractionated heparin versus low molecular weight heparin), patient type (surgical versus medical) and female sex.[6] A study compared unfractionated heparin (UFH) during or after cardiac surgery to UFH after orthopedic surgery and low molecular weight heparin (LMWH) after orthopedic surgery.[6] The study found that both UFH and cardiac surgery were risk factors for developing HIT. IgG antibodies were also more likely to form in patients undergoing cardiac versus orthopedic surgery; however in patients without antibody formation, those undergoing orthopedic surgery were more likely to develop HIT.[6]

The pathophysiology of HIT was first described in the 1970s, occurring as a consequence of antibodies to Platelet Factor 4 (PF4).[7] PF4 has been shown to neutralize the action of heparin. IgG antibodies that form against the PF4-heparin complex lead to the creation of an immunocomplex which binds to the surface of platelets and monocytes, and provokes activation by crosslinking FcgIIA receptors.[8] This causes platelet activation and aggregation, as well as generation of microparticles with procoagulant activity.[9] Microvascular endothelial cells are activated, resulting in the release of interleukin-6, von Willebrand factor, and other adhesion molecules.[10] Along with this, monocyte activation promotes formation of tissue factor (TF) - a glycoprotein interacting with plasma factor VII/VIIa. The TF/Factor VII Complex enables the initiation of the coagulation cascade via the proteolytic activation of factors IX and X causing thrombin formation.[11]

The thrombocytopenia that occurs in HIT is moderately severe even though bleeding complications are less common with most of the clinical manifestations occurring due thrombin formation.[11] HIT is diagnosed based on clinical criteria since laboratory testing results often take a longer duration of time. Diagnostic criteria of HIT include: (1) the patient having a normal platelet count prior to commencement of heparin, (2) thrombocytopenia with a drop in placement count by 30% or 50% from baseline, (3) onset of thrombocytopenia 5−10 days after initiation of heparin, (4) exclusion of other causes of thrombocytopenia (5) recovery of platelet count after cessation of heparin, (6) acute thrombotic event, (7) HIT antibody seroconversion.[12] 4T score is one of the screening techniques for HIT, the other screening technique is HIT expert probability (HEP) scoring.

There are two types of assays to detect antibodies for HIT.[13] Commercial enzyme immunoassays test for antibodies reactive against PF4/heparin or PF4/polyvinyl sulfonate.[10] ELISA tests are very sensitive (91%−97%). In contrast, platelet activation analysis detects antibodies upon their platelet activating properties. The gold standard is the 14-C serotonin release assay.[10] A positive test is strongly associated with thrombocytopenia starting five days or more after heparin exposure.[14] Heparin induced platelet aggregation is yet another test which can be used to diagnose HIT.[13] Although this test has a high specificity, it has low sensitivity to detect positive cases.[13]

Management of HIT involves utilization of alternative agents for anticoagulation including direct thrombin inhibitors (DTI), direct factor Xa inhibitors and fondaparinux. More recently, direct oral anticoagulants (DOAC) have gained more popularity for treatment of HIT.[15] Argatroban has been approved by the FDA for treatment of HIT with and without thrombosis, as a continuous infusion.[16] Argatroban use in HIT has been criticized as it requires frequent PTT monitoring, often in a critical care setting where an underlying coagulopathy may lead to PTT confounding and subsequently underdosing. Additionally, since argatroban affects the INR, care must be taken when transitioning the patient to warfarin for longer-term anticoagulation.[17] Fondaparinux is a synthetic pentasaccharide and Factor Xa inhibitor that is administered subcutaneously. It has been frequently used off-label for treatment of HIT.[15] A rare side effect of an Fondaparinaux is cross reactivity with HIT antibodies, which has caused controversy about its usage in management of HIT.[18] DOACs include factor Xa inhibitors rivaroxaban and apixaban as well as the DTI dabigatran. DOACs, in particular rivaroxaban, have gained popularity for off-label treatment of HIT. This is mainly due to short onset of action, no necessity for serum monitoring and ease of administration.[15] A recent systematic review suggested that DOACs appear to be a viable, safe option to treat HIT following an initial short course of parental therapy with a non-heparin anticoagulant.[19] When warfarin is the long-term anticoagulant of choice following resolution of HIT, it is important to bear in mind that initiation of vitamin K antagonists should not be undertaken prior to the platelet count recovering to ≥150,000 platelets/uL. Additionally, transitioning to warfarin requires a period of overlap with a non-heparin anticoagulant.[15]

Platelet transfusion should be avoided in HIT unless there is bleeding or high risk of bleeding. In general if possible, heparin should be avoided in patients with a history of HIT. However in patients absolutely requiring heparin, such as those undergoing vascular surgeries or hemodialysis, it is possible to reintroduce this without inducing another episode of HIT. Clinical trials have been lacking on

this topic. However, re-exposure to heparin may be possible at a later date, based on multiple factors.[15] Anti PF4 antibodies are transient, and a patient with a remote history of HIT who currently tests negative for anti- PF4 antibodies, can be exposed to heparin for a duration of less than 4 days.[17]

Though delayed onset HIT is the most likely cause of arterial and venous thrombosis in our patient, other inherited causes needed to be ruled out. Of the inherited causes factor V Leiden mutation and the prothrombin gene mutation, which together account for 50 to 60 percent of cases.[20] Defects in protein S, protein C, and antithrombin (formerly known as antithrombin III {AT III}) account for most of the remaining cases.[20] Based on our patients laboratory test she did have a deficiency of Anti-thrombin III at 51% activity. However this test was done already having developed acute thrombosis, which could lead to a transient drop in AT III activity level. Based on several studies done on healthy donors they found that AT III deficiency occurred in 1 in 200 to 1 in 600 individuals. One study recalled about 60 individuals and retested for AT III activity level and found that only 3 of them retested for reduced activity.[21] Given these findings the patient was managed as a patient of HIT.

4. Conclusion

Thrombocytopenia with vascular thrombosis is a serious and potentially life-threatening complication of heparin pharmacotherapy. A trend of decreasing platelet count with clinical features of thrombosis should raise suspicion for HIT, warranting further investigation. Routine dopplers of peripheral pulses in patients treated with heparin may also be of value, especially in cases of delayed-onset HIT. Prompt recognition and treatment of HIT can be life-saving. DOACs are emerging as favoured therapy for HIT. Heparin reexposure can be possible if the antibodies are no longer present and if duration of exposure is shortened.

Conflicts of interest statement

There is no conflict of interest.

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