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Case Report

Managing Heparin induced Thrombocytopenia in patients who are undergoing Left Ventricular Device Placement procedure and ultimately Heart transplant

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Abstract

Heparin induced thrombocytopenia (HIT) is a complicated disease that arises from an autoimmune attack against platelets. Heparin that is administered in a patient with HIT forms a complex with Platelet factor-4 (PF4), which is found on the surface of platelets. This complex leads to a Type III Hypersensitivity reaction where IgG antibodies bind to the Heparin/PF4 complex. The platelet-IgG complex subsequently becomes a target for destruction by the spleen. Platelet destruction eventually results in thrombocytopenia five to ten days following heparin exposure. The severity of the resultant thrombocytopenia can range from bruise-like discoloration of the skin all the way to hemorrhagic stroke in the most severe cases. Fragments of the destroyed platelets can further induce the activation of additional platelets, which lead to a thrombotic state. As a result of the recurrent thromboses, patients can develop a deep venous thrombosis (DVT) which can progress into a pulmonary embolism in severe cases. Full understanding of this phenomenon is essential in management of patients who develop this condition.

Keywords: Heparin, Thrombocytopenia, Autoimmune, Hypersensitivity, Spleen, Thrombosis

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) remains an important diagnosis to consider in hospitalized patients who develop signs and symptoms of Thrombocytopenia after administering Heparin [1]. HIT is an immune-mediated prothrombotic disorder caused by antibodies to platelet factor 4 (PF4) and heparin, which creates a complex [1][7]. The pathogenic antibodies to PF4/heparin complex bind and activate cellular FcγRIIA on platelets and monocytes to propagate a hypercoagulable state culminating in life-threatening thrombosis [2][4]. The complex can also be a target for destruction by the spleen, which creates the process of thrombocytopenia [7]. It is now recognized that anti-PF4/heparin antibodies develop commonly after heparin exposure, usually five to ten days after exposure, but only a subset of sensitized patients progress to life-threatening complications of thrombocytopenia and thrombosis [2].

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In a patient showing signs and symptoms of HIT, heparin must be stopped immediately, and confirmatory tests should follow to confirm the diagnosis**.** If HIT is not detected in a timely manner, it can be a catastrophic event as mortality secondary to thrombus is generally cited as 5%–10%, with some reporting mortality as high as 20% among HIT patients [3]. Two important tests are usually done to diagnose HIT. The first is anti-PF4 Solid Assay and the second is Serotonin Release Assay (SRA).

The anti-PF4 assay is an ELISA test that detects the presence of anti-PF4–heparin antibodies. This immunoassay can be performed by most laboratories routinely and rapidly and has a high sensitivity (>99%), thereby making it ideal for use as an initial screening test for HIT [3]. The assay is incapable of determining whether the detected antibodies can initiate the process of thrombocytopenia thus leading to a low specificity (30%–70%) for identifying HIT [4]. Additionally, patients can develop IgG antibodies that do not progress to thrombocytopenia or thrombosis. The specificity of the assay can be improved significantly by obtaining an optical density (OD). If the OD is high enough it can help determine whether the IgG antibodies are pathological. This Immunoassay have the advantage of being able to be performed by most laboratories routinely and rapidly and has a high sensitivity (>99%), thereby making them ideal for use as an initial screening test for HIT [3][5].

A Serotonin Release Assay (SRA) has a greater specificity than the ELISA test while maintaining an equally high sensitivity. This is due to the Serotonin Release Assay's ability to evaluate the properties of the antibodies it tests [4]. The SRA is currently the gold standard for diagnosing HIT [3]. The basis of the SRA involves mixing the patient's plasma with Heparin. If platelets and the antibodies aggregate in the reaction, serotonin is released thus confirming the diagnosis.

We report a case of HIT in a patient who underwent extensive cardiac procedures that require anticoagulation. The management of this case is more complicated than managing HIT alone.

CASE PRESENTATION

A 44-year-old female, six weeks post-partum, with a history of non-ischemic cardiomyopathy (NICMP) presented with shortness of breath and abdominal swelling. Extensive work up, showed heart failure with an ejection fraction of 10%. Medical management improved the EF to 25-30% range. The patient had an Automatic Implantable Cardioverter Defibrillator (AICD) placed in 2011 (single chamber) and was doing well for 6 year. In 2017, following recurring exacerbations, the AICD was updated to non-single/dual coil.

The patient had a history of recurring Atrial Fibrillation (AF) with rapid ventricular rate which was managed with Coumadin. The patient has obstructive sleep apnea, in addition to history of Left Ventricular apical thrombus, dyslipidemia, and morbid obesity and heart failure exacerbations. She was transferred for further evaluation for advanced heart failure therapies and management.

The patient was planned to have a Left Ventricular Device procedure and ultimately a heart transplant due to her heart failure condition. During her inpatient stay, Coumadin was changed to heparin on admission. Baseline platelets on arrival were 150K-170K, which was down trended over to 35K (fall began on day 10 after heparin exposure). Platelet count was confirmed at 29K in citrated tube. She was changed to Argatroban on and the platelets were improving afterwards.

At her early inpatient stay, the Serotonin Release Assay (SRA) and the anti-PF4 solid phase assay were both negative. Repeat SRA and anti PF4 assay were sent again, and the results were pending at that time. The patient denied any history of thrombocytopenia that she knows of. She also denied any spontaneous bruising or bleeding. She reported heavy periods normally since starting Coumadin. Her only new medications within the last weeks were Sotalol and Bumex. The patient has been on the following medications that could have an adverse effect on platelets and could potentially cause thrombocytopenia. These medications were Methotrexate, Entresto, Famotidine and Aldactone. She believed her only recent exposure to Lovenox was 1 Lovenox injection several months prior to current presentation. She reported that this was her 4th hospital admission this year and was kept on Coumadin during prior admissions.

A repeat PF4 was sent, and results were strongly positive, with OD 2.8, also SRA test was positive as well, making HIT a more relevant diagnosis for the thrombocytopenia. The plan was to continue anticoagulation with Argatroban until platelets count are consistently >100K, and then transition to non-vitamin K antagonist oral anticoagulants (NOAC) with Apixaban (Factor Xa inhibitor).

A month later, the patient was set to have a Left Ventricular Assistance Device (LVAD) procedure on. Before her LVAD procedure, Argatroban was given until platelets count are consistently >100K, and then she was transitioned to non-vitamin K antagonist oral anticoagulants (NOAC) with Apixaban (Factor Xa inhibitor). Platelets going into the procedure were 159k, and the INR was 1.67.

During the procedure heparin was completely avoided and full anticoagulation was achieved by administration of IV Bivalirudin This configuration was used for about 90 minutes. The Cardio-Pulmonary-Bypass machine was at 1 lit/min to proceed with the ultrafiltration process to remove Bivalirudin from the blood and reverse anticoagulation. An insertion of a left femoral vein dialysis catheter was performed, and there was continuous bleeding, so the patient was found to require further removal of Bivalirudin, which was achieved by using the CPB machine for several hours to correct anticoagulation and clear the Bivalirudin from the system. After the surgery the patient was then transitioned to Argatroban and then bridged to Coumadin with an INR goal of 2-3. The patient was discharged with stable hematological conditions and there were no signs of HIT complications.

The LVAD procedure was a bridge to heart transplant. The patient was evaluated for a heart transplant and had the procedure six months later. Four months following surgery (> 100 days since HIT dx): Labs have returned with negative SRA; however, heparin antibodies remained positive (OD 0.75). Given that she has not been exposed to heparin for several months and she still has heparin antibodies present, the decision at this point was to continue to manage the patient with Argatroban rather than preemptive plasmapheresis or IVIG prior to procedure. The patient followed the same plan with Argatroban given instead of heparin. To reverse the Coumadin the patient was started on Vitamin K 10mg IV x1 for reversal of INR (last Coumadin 6mg dose was about four months earlier). Platelets going into the procedure were 166k, and the INR was 2.5. During the procedure heparin was completely avoided again and full anticoagulation was achieved by administration of IV Bivalirudin (bivalirudin 250 mg [1.5 mg/kg/hr.] + premix saline diluent 50 ml). The CPB machine with the ultrafiltration process was used to remove Bivalirudin from the blood and reverse anticoagulation.

The patient continued to have bleeding POD#1, so multiple blood products were given due to increased bloody output from mediastinal tube. The patient received overall 5 units of blood (2800 ml from cell saver), along with factor VII (factor VIIa recombinant 1000 mcg (1 mg Inj), Platelets (416ml), FFP (715 ml), and cryoprecipitate (200ml), and INR was closely monitored afterwards.

Chest Closure was delayed POD#2 to ensure that the patient stopped bleeding and hemodynamically stable. INR POD#2 was 1.19, platelet count was 113K, INR was 1.31. Hematocrit was 30.6, and Hemoglobin was significantly increased overnight to 14.3 due to the blood products that were given. To improve the thrombocytopenia, CellCept was reduced from 1 g bid to 500 mg bid. POD#2. Platelets continued to decrease significantly to 54K, INR was 1.29, Hematocrit was 28.5, and Hemoglobin was 10.1. The patient continued to be hemodynamically stable and platelet

count increased to 79K POD#7 and 156K on POD#8. During post-op ambulation was encouraged daily to minimize the risk of developing DVT. On POD#9 the patient was transferred from SICU to normal inpatient care. On POD#28 the patient was hemodynamically stable and was discharged from the hospital. Patients condition was stable the following eight months with no evidence of complications, after which he was lost to follow up.

DISCUSSION

On June 1, 1957, Rodger E. Weismann, an Assistant Professor of Clinical Surgery at the Dartmouth Medical School, and his Resident in Surgery, Dr Richard W. Tobin, described 10 patients who developed arterial embolism while receiving systemic heparin therapy. The first embolic event was a femoral artery embolic occlusion, which occurred in a 62-year-old woman who was receiving heparin (DVT). Three days after successful femoral embolectomy, and while continuing to receive heparin, she developed sudden occlusion of the distal aorta requiring distal aortic and bilateral iliac embolectomies. Multiple thromboembolic events were observed in 9 of the 10 patients reported. Six patients died because of the thromboembolic events, and 2 survivors underwent above-knee amputation [5]. The arterial emboli began on average 10 days after commencing heparin treatment. This noted the hallmark of Heparin induced thrombocytopenia (HIT), a delay of approximately 1 week from initiation of heparin to onset of its thrombotic manifestations. This event prompted the start routine platelet checks upon administering heparin [5][8].

Heparin is still widely used for thromboprophylaxis or treatment in many clinical situations, including cardiovascular surgery. Recent data show that up to 8% of heparinized patients will develop the antibody associated with HIT, and that approximately 1–5% of patients will progress to develop HIT with thrombocytopenia, suffering from venous and/or arterial thrombosis in at least one-third of cases [6].

The platelet factor-4 (PF4) is a chemokine that is contained in platelet α-granules. PF4 is not immunogenic in its primary form. Conformational PF4 changes are needed to expose a neo-epitope, which is the HIT antigen. These changes occur by the formation of complexes between PF4 and negatively charged molecules, especially heparin and other glycosaminoglycans (GAGs) [7][1]. This activates the complement system leading to the deposition of C3/C4 on the complexes. This subsequently initiates the adaptive humoral immune response where anti-PF4/Heparin complex antibodies start being produced [7] [11]. Those antibodies mark the complex for destruction by the spleen. The degranulation of those destructed platelets leads to aggregation of other platelets which induces the thrombotic events [2][4] [7]. Arepally and Padmanabhan described in detail the complex multi-cellular process involved in formation and effect of HIT as an interaction between platelets antibodies with neutrophils, monocytes, and endothelial cells (**Figure 1**) [11]. HIT is different from immune mediated drug reaction. Adam Cuker and group described the clinical presentation and features of HIT versus immune mediated drug reaction and listed detailed explanation (**Table 1**) [12].

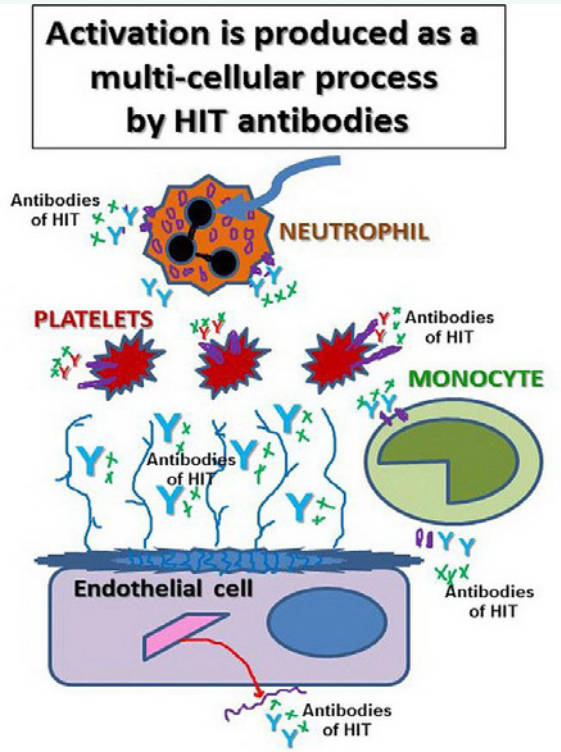

Figure 1 Activation is a multi-cellular process by HIT antibodies

Adapted from: Gowthami M. Arepally and Anand Padmanabhan. A Focus on Thrombosis. Heparin-Induced Thrombocytopenia. Arteriosclerosis, Thrombosis, and Vascular Biology. Volume 41, Issue 1, January 2021; Pages 141-152 https://doi.org/10.1161/ATVBAHA.120.315445 [11]

Table 1: **HIT versus immune mediated drug reaction.** Adapted from Adam Cuker and Douglas B. Cines. How I treat heparin-induced thrombocytopenia. BLOOD, 8 MARCH 2012-VOLUME 119, NUMBER 10 [12].

FEATURES OF HIT	EXPLANATION OF FEATURES
Higher incidence after surgery or trauma	**More platelet activation and PF4 release leading to larger immune complex**
Higher incidence with unfractionated heparin	**Larger heparin molecule causing larger immune complexes**
Paradoxical thrombosis	**Activation of platelets and monocytes by immune complexes**
Onset may follow heparin discontinuation	**Damage to endothelial cells by antibodies bound to PF4/ heparin sulfate complexes or heparin-independent antibodies**
Lack of recurrence with heparin re-exposure	**Complex pathophysiology, antibody formation necessary but sufficient to cause clinical disease**

The result of the thrombocytopenia and the thrombosis can have various effects depending on the severity. If a patient starts having signs and symptoms of HIT, heparin must be stopped immediately, and confirmatory tests should follow to confirm the diagnosis. First a clinical diagnosis should be done. This depends on a 4T score which includes thrombocytopenia, timing of platelet count fall, thrombosis, and other causes of thrombocytopenia [3]. This score must be confirmed by lab values such as the anti-PF4 assay and the Serotonin Release Assay. Serotonin Release assay is considered the gold standard diagnostic test for HIT [3][4].

Management of HIT follows two major goals: preventing any additional platelet activation and providing adequate therapeutic anti-coagulation until the threat of thrombosis returns to baseline. The primary initial intervention in a patient with suspected acute HIT is the rapid cessation of all heparin [8]. Termination of heparin is followed by the initiation of an alternative non-heparin anticoagulant like Argatroban, Bivalirudin, Danaparoid (available outside U.S), Fondaparinux, or a direct oral anticoagulant (DOAC). The choice of agent is dependent on drug factors (cost, half-life, route of administration and patient factors (renal & hepatic function) [9]. Regardless of whether a thrombotic event has occurred or not, a therapeutic dose of anticoagulation must be administered. Exceptions only apply in cases where bleeding risk is increased [8]. The short half-lives of Bivalirudin and Argatroban allow the anticoagulation to be reversed rapidly in the setting of an invasive procedure. Bivalirudin is the preferred non-heparin anticoagulant in patients with acute HIT who require urgent cardiac surgery. In non-urgent cases, surgery must be delayed until the HIT has resolved and HIT antibodies are negative [10]. IVIG is only used in cases of HIT where there is no reported Heparin exposure [8].

This case was approached similarly to the 2012 American College of Chest Physicians management guidelines [10]. Placement of the LVAD was not done until two months after the initial HIT presentation. The patient was then given Argatroban pre-operatively to replete the platelet levels. This was followed by anticoagulation with Bivalirudin intra-operatively. In the post-operative period, Argatroban was restarted until the INR reached a sufficient level to bridge to Warfarin. The heart transplant five months later was also managed with Argatroban pre-operatively with Bivalidrun in the intra-operative period. Fresh blood products were given in the post-operative period to ensure hemodynamic and hematologic stability.

We report this case of HIT in a patient who underwent extensive cardiac procedures that required anticoagulation. The management of this case is more complicated than managing HIT alone. We summarized the current understanding of thrombosis in heparin-induced thrombocytopenia with attention to its clinical features, cellular mechanisms, and its successful management in a unique clinical setting.

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