Argatroban-refractory, Heparin-induced Thrombocytopenia after Coronary Intervention with Radial Artery Occlusion

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Abstract Heparin induced thrombocytopenia (HIT) is serious disorder that occurs in a small percentage of patients following exposure to heparin. HIT can further be classified into two types: HIT type 1 and type 2. Type 2 HIT is a potentially life threatening with clinically significant outcomes. It presents with thrombocytopenia and evidence of thrombus formation in the presence of antibody formation. Additionally, several variations of HIT exist, including delayed onset HIT and refractory HIT, known collectively as autoimmune HIT (aHIT). Here we present a case of delayed onset and refractory HIT in a patient with little heparin exposure, discovered only after cardiac intervention for suspected STEMI. Significant thrombotic events occurred thereafter, including radial artery stenosis and intracardiac thrombus. Treatment with argatroban was ineffective. Significant resolution of thrombocytopenia was seen several weeks after infusion with IVIG, thus depicting further suspicion for refractory HIT. IVIG for aHIT treatment is traditionally chosen only if the disease process is refractory to other anticoagulation efforts due to the potential risk for increasing thrombotic risk with IVIG infusion. Our case illistrate the rare presentation of aHIT and the use if IVIG to successfully treat thrombocytopenia in refractory HIT.

Keywords: heparin-induced thrombocytopenia, radial artery occlusion, coronary intervention complications

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1. Introduction

Heparin induced thrombocytopenia (HIT) is a life-threatening disorder that occurs in a small population of people after exposure to heparin. Drug reactions typically occur after an average of 5-10 days of exposure and occurs as a result of the formation of HIT antibodies. Treatment of HIT typically involves discontinuation of heparin products and the utilization of non-heparin anticoagulation medications. Platelet counts will return to normal or pre-HIT levels in 3-7 days. [1]

In certain case, platelet levels do not improve and remain refractory to standard treatment methods. These cases of refractory HIT along with delayed onset and spontaneous HIT have recently been collectively labeled as "autoimmune HIT" (aHIT) [3]. Treatment for aHIT was discussed as early as 1994, where researchers determined that IVIG was effective at treating refractory HIT [13]. Although, shown to be effective, IVIG use has also been implicated in thrombus formation and increasing likelihood of thrombotic events [15]. Case reports of patients with aHIT are few in number, however of those that exist, it seems that those treated with IVIG

responded well and did not develop further thrombotic events [13,14].

Here we discuss a case of aHIT, where a 48yo male developed multiple thrombi after exposure to minimal amounts of heparin. Despite recognition of HIT and initiation of treatment, the patient's platelet levels remained low and did not respond to treatment, thus prompting a possible diagnosis of aHIT. Only several weeks after treatment with IVIG did platelet levels return to baseline.

2. Case Presentation

A 48 year-old male with a past medical history of hypertension, chronic kidney disease, active smoking history, and multiple myeloma presented with sudden onset chest pain one week after stem cell harvesting. He described it as severe crushing substernal chest pain, radiating to his left arm and jaw. Pain was associated with diaphoresis, dyspnea and nausea. He reported that the pain woke him up from sleep. He also endorsed a one week history of decreased exercise tolerance from 3-4 blocks down to less than one block. He denied orthopnea, paroxysmal nocturnal dyspnea or peripheral edema. In the

ED, physical examination revealed a well developed male, anxious, in mild distress, due to chest pain. He was afebrile with a blood pressure of 97/65 and a heart rate of 56. His electrocardiogram showed sinus bradycardia and ST segment elevation in leads II, III, aVF (Figure 1). His troponin I was elevated to 0.74 ng/L [Normal <0.04 ng/L], white blood cells were 28K/cmm (4K – 11K), hemoglobin 17.4g/dL (13-18), hematocrit 54% (40 – 52), platelets 26K/cmm (150 – 450). He was immediately started on aspirin and clopidogrel and a STEMI code was initiated. He was immediately taken for a cardiac catheterization which revealed 100 % stenosis in the distal segment of posterior descending artery (PDA). The lesion was associated with a large filling defect consistent with thrombus. An attempt of balloon angioplasty was unsuccessful (Figure 2, Figure 3). Post cardiac catheterization he experienced an episode of altered mental status with polymorphic ventricular tachycardia and asynchronous jerks lasting for 10 seconds. Repeat lab work revealed that platelets were dropping. His hematologist was contacted and reported that the patient had received 1 unit of platelet transfusion 5 days prior to presentation. Transthoracic echocardiography revealed ejection fraction estimated in the range of 65% to 70% with hypokinesis of the basal inferior wall(s). Doppler parameters were consistent with abnormal left ventricular relaxation (grade 1 diastolic dysfunction). His right atrium (RA) showed a medium-sized, flat mural mass, measuring 21 mm x 15 mm in the lateral right atrial cavity. The mass was representative of a myxoma, thrombus or an artifact (Figure 4). A decision was made to hold antiplatelets and to give another unit of platelets due to rapidly dropping platelets. On the following day, he was found to have non palpable right radial pulse with good ulnar pulse. He was sent for right radial artery duplex study which showed radial artery occlusion (Figure 5, Figure 6). Heparin-induced thrombocytopenia (HIT) type II was suspected at this time. Laboratory tests were requested and heparin induced platelets antibody, antiplatelets factor 4, was 2.99 OD units (0.00-0.3) and serotonin release assay for heparin-dependent platelet activation was 68% (0-20). Argatroban infusion was started. Over the next few days, right radial pulse was regained and platelets started to rise, however, the response to argatroban was inadequate. His case was considered as heparin-independent, argatroban refractory HIT. The patient was then started on reduced dose of IVIG (500 mg/kg/day) given recent history of STEMI and renal disease. Treatment was continued for 4 days along with prednisone 60 mg daily. Platelet counts did not show an adequate response initially. Bone marrow biopsy was performed, which revealed no significant immunophemotypic abnormalities. He was sent for transesophageal echocardiography which showed the chemo port venous catheter with either fibrinous debris or thrombus formation on the tip. Additionally, a large, irregular mass adjacent to the free wall measuring 1.4 x 1.4 cm was seen and raised suspicion for possible thrombus (Figure 7). The patient was continued on both argatroban and warfarin for 5 days until his INR became 4, after which the argatroban was stopped. Platelets improved to the normal range after 40 days of presentation (Figure 8).

3. Discussion

Heparin Induced Thrombocytopenia (HIT) is a life and limb-threatening complication resulting after exposure to heparin products [1]. HIT has been reported after exposure to any heparin dose, schedule and administration route [2,3]. Patients can also develop HIT regardless of their prior exposure to heparin, however is commonly seen after exposure to unfractionated heparin.

Historically there are two major types of HIT; type I, which is described as a mild transient drop in platelets, that occurs within the first two days of heparin exposure. Type I is non-immune mediated, and it occurs due to the direct effect of heparin on platelets [4]. This form is not considered clinically significant and is not associated with thrombosis. HIT Type II is due to antibodies to platelet-factor-4 (PF4) complexed to heparin, referred to HIT-antibodies [5]. This type is considered to be significantly associated with thrombotic events.
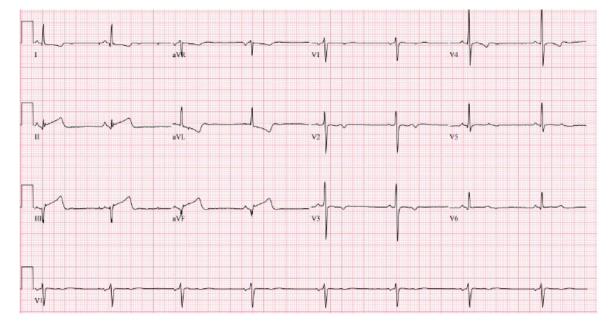

Figure 1. EKG demonstrating sinus bradycardia with STEMI in leads II,III,aVF (Inferior infarction) with acute T wave abnormality.
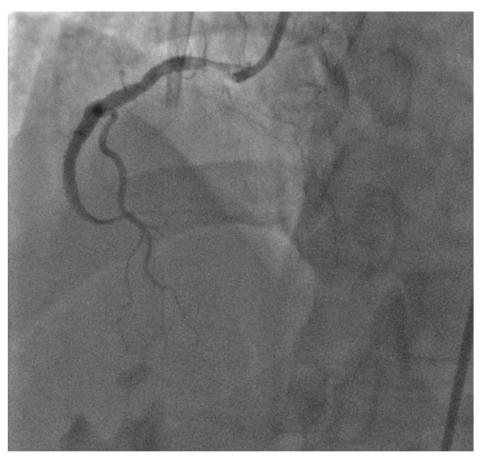
Figure 2. Cardiac catheterization revealed 100 % stenosis in the distal segment of posterior descending artery (PDA). The lesion was was associated with a large filling defect consistent with thrombus. An attempt of balloon angioplasty was unsuccessful

Figure 3. Cardiac catheterization revealed 100 % stenosis in the distal segment of posterior descending artery (PDA). The lesion was was associated with a large filling defect consistent with thrombus. An attempt of balloon angioplasty was unsuccessful
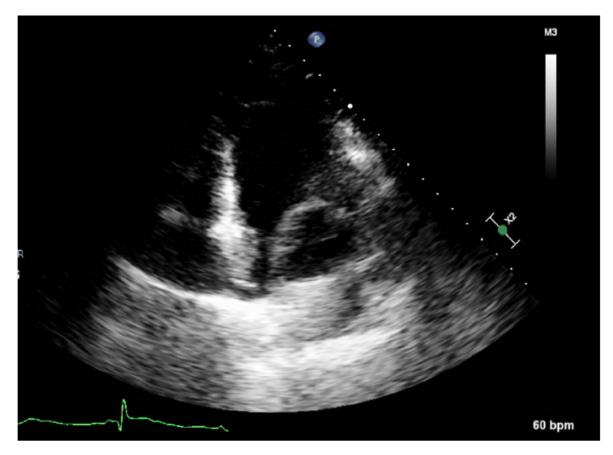
Figure 4. Transthoracic echocardiography revealing a medium-sized, flat mural mass, measuring 21 mm x 15 mm in the lateral right atrial cavity. The mass may represent a myxoma, thrombus or an artifact

Figure 5. Right radial artery duplex study which showed radial artery occlusion
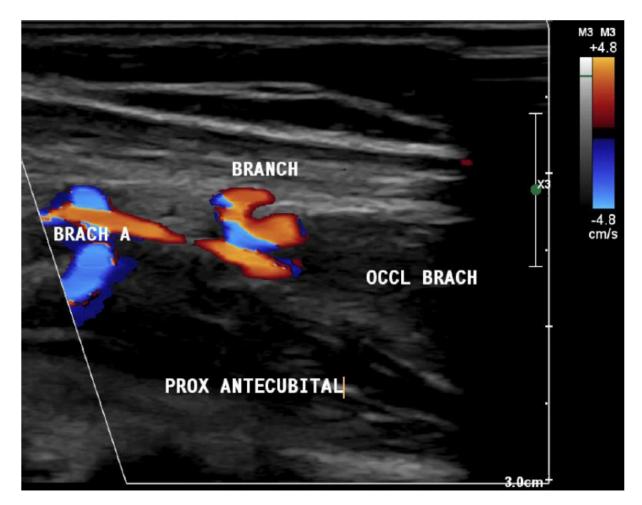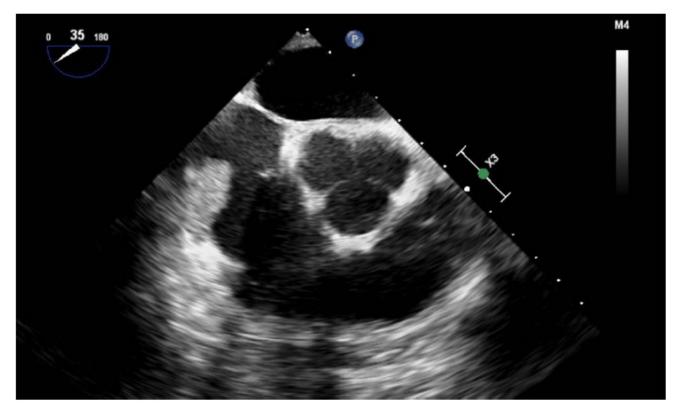
Figure 6. Right radial artery duplex study which showed radial artery occlusion

Figure 7. Transesophageal echocardiography revealed chemo port venous catheter which has either fibrinous debri or thrombus on its tip. There was a large, irregular mass adjacent to the free wall measuring 1.4 x 1.4 cm, which is probably thrombus
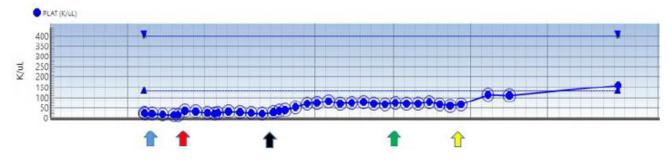
Figure 8. Platelets trend over the course of treatment. Blue arrow: presentation with STEMI, Red arrow: radial artery occlusion, HIT diagnosis and starting argatroban, Black arrow: starting IVIG, Green arrow: Bone Marrow biopsy and bridging with warfarin, Yellow arrow: Discontinuing argatroban

Greinacher A. et al, described other variants of immune-mediated HIT that can occur in the presence or absence of heparin. These were collectively referred to as autoimmune-HIT (aHIT). Autoimmune-HIT variants include; Delayed-onset HIT, refractory HIT and spontaneous HIT [3]. aHIT is characterized by a significant drop in platelets, occurring after a prolonged exposure of 10-17 days of heparin. The average nadir platelet count is approximately 60,000/microL, with platelet counts below 20,000/microL being rare. Severe thrombocytopenia, although not typically seen in HIT, has been described in 50% of patients with delayed onset HIT. Patients with aHIT have a pro-thrombotic state, causing venous or arterial thrombosis [5,6,7,8]. Rarely, aHIT can also occur with minimal exposure to heparin such as heparin flushes used for intravascular catheters. This helps to explain how HIT can occur with such small quantities of heparin [3].

Diagnosis of HIT requires a high-index of clinical suspicion and laboratory evidence. The 4-Ts are used to estimate the likelihood of HIT. A score of intermediate or high probability would encourage clinicians to perform confirmatory testing [9]. ELISA (Enzyme Linked Immune Sorbent Assay) is the most widely used confirmatory test. An Optical Density (OD) result of more than 2.00 gives a probability of >90% [10]. Other tests used to diagnose HIT include the serotonin release assay, which has been considered as the gold standard test, having a sensitivity and specificity of more than 95% [11].

Once diagnosed, treatment of HIT Type I and Type II involves discontinuation of heparin products & initiating anticoagulation. Type I can be managed expectantly. Heparin cessation alone is not sufficient since patients with HIT remain at risk for subsequent thrombosis [9]. Anticoagulantion options include parenteral argatroban, bivalirudin, fondaparinux or danaparoid or oral Direct Oral Anticoagulants (DOAC) [9]. Warfarin should not be used as the initial anticoagulant in patients with HIT. Patients can be transitioned to warfarin after platelet counts rise to at least 100,000/microL. It is recommended that a minimum of five days of overlapping therapy occur before continuing warfarin alone [9]. Duration of anticoagulation has not been evaluated by large prospective studies; however, several societies have agreed on a general rule for duration. Duration of treatment is dependent on whether a thrombosis event occurred or not; 1 month if no thrombosis occurred and 3 months in the presence of thrombosis [9].

Managing patients with aHIT can be challenging. A number of cases have been recognized to be refractory to traditional anticoagulation and required alternative treatment such as Intravenous Immunoglobulins (IVIG) [6]. The use of IVIG to treat HIT was described for the first time more than 25 years ago, where it was noted to cause abrupt platelet recovery after treatment [12].

In the last decade, with increasing recognition of aHIT, use of IVIG has been more frequent. Greinacher et al and Padmanabhan et al found that IVIG worked by preventing platelet activation by HIT antibodies in vitro [13,14]. The lack of impact of these reports on clinical practice is illustrated by the absence of mention of this therapeutic option in major guidelines and reviews. In fact, an expert panel recommended against the management of HIT, a pro-thrombotic disorder, with IVIG. They recommended that treatment should be focused on decreasing the risk of thrombotic events and that IVIG could potentially increase the risk of thrombosis and therefore should not be used [15]. However, our literature review since that publication, has shown no cases of IVIG-induced thrombosis occurring after IVIG treatment for aHIT. Tvito et al. summarized only 12 cases of aHIT treated with IVIG. Most of the cases in this review were refractory to traditional anticoagulation, direct thrombin inhibitors, and also showed persistence of thrombocytopenia (prior to administration of IVIG). In all 12cases, platelet counts recovered after IVIG administration. We identified an additional 5 cases, discussing a total of 7 patients, who had complicated aHIT. All of these cases demonstrated significant response to IVIG confirming the results of the Tvito review [6].

Our case demonstrated an all HIT variants spectrum, described by Greinacher et al [3]. Our patient had delayed-onset HIT as he developed 3 known thrombotic events 1 week after minute heparin exposure during stem-cell harvesting. Events included acute MI, intracardiac thrombus and radial artery thrombosis. Spontaneous HIT is also a possibility as the patient had minute heparin exposure in the setting of heparin flushes during stem cell harvesting. Adittionally, the patient exhibited refractory HIT as he showed improvement with a platelet count rising above 100'000/microL 5 weeks after the exposure to heparin and 3 weeks after IVIG treatment.

4. Conclusion

Our case supports the growing evidence that IVIG is a helpful supplemental treatment to increase platelet count and interfere with activation of heparin- PF4 antibodies in cases of severe persistent HIT.

Acknowledgements

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