

# Heparin Induced Thrombocytopenia (HIT) without Thrombocytopenia-A case report and a literature review

I Ahmed, M Naglak, H Rashid

## Citation

I Ahmed, M Naglak, H Rashid. *Heparin Induced Thrombocytopenia (HIT) without Thrombocytopenia-A case report and a literature review*. The Internet Journal of Hematology. 2008 Volume 5 Number 2.

## Abstract

HIT is a well known complication of heparin therapy. Typically patients get low platelet counts after an exposure to heparin therapy and may have associated thrombotic complications. We present a case of a patient who was diagnosed with HIT and did not have an absolute or a relative drop in his platelet count.

## INTRODUCTION

HIT is a well known complication of heparin therapy. Typically patients get low platelet counts after an exposure to heparin therapy and may have associated thrombotic complications. We present a case of a patient who was diagnosed with HIT and did not have an absolute or a relative drop in his platelet count.

## HISTORY

A 65-year-old white male presented to our hospital with chief complaints of left leg swelling and pain for 3 days. On review of symptoms he also admitted constant dull substernal chest pain associated with mild shortness of breath at rest. His chest discomfort was non pleuritic and non exertional. He denied fever, chills, cough, paroxysmal nocturnal dyspnea and orthopnea. The patient gave a history of air travel ten days prior to his presentation to the emergency room. He had a four hour flight while returning from a vacation; he was seated in the chair for the entire flight because of turbulence.

His past medical history was significant for coronary artery disease, hypertension and dyslipidemia, however, there was no previous history of thromboembolism. He was last hospitalized about a year ago for a myocardial infarction, at that time he received a coronary stent. He was an ex-smoker with a 10 pack year smoking history; he quit smoking 5 years ago. He drank alcohol only on social occasions. There was no family history of thromboembolism.

## PHYSICAL EXAMINATION

On examination in the emergency room he looked

uncomfortable with a temperature of 98.6 F, heart rate of 96/minute, blood pressure of 130/70, respiratory rate of 20/minute and oxygen saturation of 97% on room air. His respiratory, cardiovascular and abdominal examinations were unremarkable. His entire left leg was swollen, firm and tender without any erythema. His right leg looked normal.

## LABORATORY AND IMAGING STUDIES

His complete blood count, basic metabolic panel and a chest x ray were all normal. His PT/INR and aPTT were also within reference range. A 12 lead EKG showed sinus tachycardia but no other changes. A doppler ultrasound of left his lower extremity showed extensive thrombosis in the superficial femoral vein and popliteal veins. A CT thorax angiogram showed multiple filling defects within the central pulmonary vessels due to bilateral pulmonary emboli.

## HOSPITAL COURSE

In the emergency department he was started on intravenous unfractionated heparin infusion after a loading dose. He was admitted under the medical service with a diagnosis of acute deep venous thrombosis and bilateral pulmonary emboli. Coumadin was started on the same day. While on intravenous heparin his platelet count was monitored regularly. The patient was up-to-date with his age appropriate cancer screenings. No further hypercoagulable work up was obtained. His hospital course remained uncomplicated and he was discharge home after eight days when his INR became "therapeutic". Intravenous heparin was overlapped with coumadin for 2 days after PT/INR were therapeutic. He was given instructions for following his PT/INR with his family doctor.

On the next day (day 9) the patient returned to the emergency room with worsening pain and swelling in his left leg. A repeat venous doppler of his lower extremities showed further propagation of his popliteal and superficial femoral vein clots. His INR was 2.2. His platelet count was 4, 35,000 K/ul. He was readmitted on the medical floor. A hypercoagulable state was suspected. Hematology services were consulted. A hypercoagulable panel was obtained which also included a HIT antibody assay. Patient's coumadin was held and he was started on intravenous argatroban given suspicion of heparin induced thrombocytopenia because of significant recent exposure to heparin. On the night of admission the patient experienced an episode of chest pain for which a thoracic CT angiogram was done, which showed increased clot burden in the pulmonary vasculature on the left side as compared to a CT scan on previous admission.

The next day (day 10), the HIT antibody ELISA assay came back positive. To confirm this, a serotonin release assay was sent to an outside laboratory. Meanwhile the patient was continued on argatroban. Results of the serotonin release assay were positive. The rest of his hypercoagulable work up came back normal. He was discharged home on coumadin without any problems.

Figure 1: Trend of platelet count during hospital stay

## DISCUSSION

This patient initially presented with acute lower extremity deep venous thrombosis and bilateral pulmonary embolisms. He was managed with intravenous unfractionated heparin and sent home on coumadin once his PT/INR became therapeutic. Given a recent travel history and the fact that he was up-to-date with his age appropriate cancer screenings, no further hypercoagulable work up was obtained. After the patient was readmitted the day after his discharge with increased clot burden in his legs and lungs, a hypercoagulable state versus coumadin failure was suspected. A hypercoagulable work up included a HIT antibody assay despite the fact that the patient did not meet the current definition criteria for heparin induced thrombocytopenia, which are 30-50% drop in platelet count or platelet count <150,000 k/ul after exposure to heparin. Interestingly, his HIT ELISA antibody was positive making diagnosis of HIT more likely which was later confirmed with a more specific functional assay.

Cases of HIT with normal platelet counts even without a relative thrombocytopenia have been reported in literature.<sup>123</sup>

Our case is an addition to this increasingly recognized form of this disease.

## HEPARIN INDUCED THROMBOCYTOPENIA

Heparin induced thrombocytopenia is a well recognized, life threatening complication of heparin therapy. This disease is caused by formation of IgG antibodies against heparin-platelet factor 4 complex. These patient classically have thrombocytopenia with platelet counts of <150,000 K/ul or a relative 30-50% drop in platelet count from baseline after exposure to heparin therapy. But patients with normal platelet counts even in the absence of relative thrombocytopenia may have this disease.<sup>123</sup>

The main risk of this disease is life threatening vascular thrombosis. It is estimated that thrombosis occurs in about 20-50% of the patients.<sup>456</sup> DVT and PE are the most common thrombotic events.<sup>7</sup> Most of the thrombotic events occur in the first week of diagnosis of HIT.<sup>7</sup> Medical and orthopedic patients tend to get venous thrombosis while post operative cardiac and vascular surgery patients tend to have both arterial and venous thrombosis at the same frequency.<sup>48</sup> The time period from onset of heparin therapy to development of thrombocytopenia is typically 4-10 days.<sup>9</sup> Patients who had recent prior exposure to heparin (within last 100 days), can develop thrombocytopenia within hours.<sup>10</sup>

## PATHOPHYSIOLOGY

When heparin is administered to a patient it can bind and form complexes with platelet factor 4 (PF4) which is a heparin binding protein released from alpha granules of platelets. These complexes may be viewed as a foreign antigen to the body and therefore result in formation of antibodies against them. Those antibodies then bind to the complexes which are attached on the platelet surfaces leading to platelet activation.<sup>11</sup>

## INCIDENCE

The incidence of heparin induced thrombocytopenia is quite variable and depends on factors like clinical context of a patient, duration of heparin therapy, route of administration and type of heparin used e.g. low molecular weight heparin (LMWH) or unfractionated heparin (UFH). Generally it occurs in about 0.5-5% of patients on heparin therapy.<sup>8</sup>

Patients at higher risk include those with recent exposure to any type of heparin (within last 100 days) and detectable Ig G heparin-platelet factor 4 antibodies, those treated for more than 4 days. Medical patients are at higher risk than surgical

patients. In surgical patients those undergoing CABG, orthopedic surgery and limb surgery are more vulnerable. Pediatric patients have a lower incidence and severity of this disease.<sup>7</sup> In a meta analysis the incidence of HIT reported was ten times more in patients being treated with UFH than those treated with LMWH.<sup>12</sup>

### **CLINICAL PRESENTATION**

Patients with HIT may be asymptomatic clinically or they can manifest with signs and symptoms of arterial and/or venous thromboembolism in different parts of the body. Symptoms of thrombosis may include those related to DVT of the upper and lower extremities, pulmonary embolism and cerebral venous thrombosis. Other thrombotic complications include stroke, MI, bowel infarction, and renal infarction.<sup>7</sup> Bleeding is rare despite low platelet counts in these patients. Other rare manifestations include acute systemic reactions, skin reactions at heparin injection sites and over disseminated intravascular thrombosis (DIC).

### **LABORATORY DIAGNOSIS**

When HIT is suspected on the basis of clinical suspicion and dropping platelet count a diagnostic work-up should be initiated. Immunologic and functional assays are currently available to help in diagnosis. Immunologic assays detect IgA, IgG and IgM heparin-platelet factor 4 antibodies, they have high sensitivities of >97% but specificity is lower, 74-86%.<sup>101314</sup> Ig G specific antibody assays have higher specificity<sup>1415</sup> but they are not available commercially.

Functional assays can measure platelet aggregation and release of C-serotonin from activated platelets. The serotonin release assays have high sensitivity and specificity of 89-100%.<sup>13</sup> However, they are costly and not widely available. A positive immunologic test and progressive rise in platelet count after stopping heparin is usually confirmatory. If the immunologic test is negative it can be repeated within 24 hours if suspicion remains high. If a repeat immunologic test is negative and platelets do not rise after stopping heparin, then an alternate diagnosis should be sought.<sup>7</sup>

### **MANAGEMENT**

Once a diagnosis of HIT is strongly suspected in the proper clinical setting, all kinds of heparin including any heparin flushes and heparin coated catheters should be stopped while laboratory confirmation is pending. In addition, alternate forms of anticoagulation should be started in patients with known thrombotic conditions and in those with isolated

thrombocytopenia without any thrombotic phenomenon.<sup>9</sup> Just stopping heparin is not sufficient because these patients continue to be in a very hypercoagulable state. Without any form of alternate anticoagulation, >50% of patients can develop thrombosis over the next few days to weeks.<sup>7</sup>

LMWH should not be started as an alternate anticoagulation because it cross-reacts with heparin-platelet factor 4 complex.<sup>9</sup> Coumadin, if started early before stabilization of platelet count, can paradoxically worsen the thrombosis presumably as a result of protein C depletion. There have been case reports of coumadin causing skin necrosis and venous gangrene of the extremities if started early before recovery of platelet counts.<sup>91617</sup>

Alternate anticoagulation agents include direct thrombin inhibitors (such as argatroban and lepirudin), and heparinoids (such as danaproid and fondaparinux). In the United States, the FDA has only approved direct thrombin inhibitors for management of HIT.

Argatroban can be used safely in patients with renal impairment because it is cleared through the liver.<sup>18</sup> Its effect can be monitored by aPTT. It has a short half life of 24 minutes in vivo.<sup>19</sup> Repeated administration of argatroban has not been reported to cause formation of antibodies, so it can be used repeatedly.<sup>20</sup> Lepirudin should be used with caution in patients with renal dysfunction because it is renally cleared and antibodies can form with repeated administration. After first exposure to lepirudin, about 30% of patients form antibodies while 70% of patients develop antibodies after repeated exposure.<sup>21</sup>

Bivalirudin is a synthetic thrombin inhibitor. It is approved by the FDA only for use in patients with or at risk of HIT who are undergoing percutaneous coronary intervention. Danaproid is a mixture of dermatan sulphate and chondroitin sulphate. It binds to antithrombin III leading to anti X-a activity. It is not approved by the FDA for use in HIT.

### **CONCLUSION**

HIT is a life threatening complication of heparin therapy. HIT can present with thrombocytopenia or with a normal platelet count. A high index of suspicion is required to diagnose this condition. Delay in diagnosis can have devastating outcomes. Early identification and treatment of HIT can prevent more serious complications associated with this disorder. Heparin use should be limited to less than 5 days and early transition to warfarin should be considered to avoid this disease.

## References

1. Hach-Wunderle V, Kainer K, Krug B, Muller-Berghaus G, Potzsch B. Heparin-associated thrombosis despite normal platelet counts. *Lancet* 1994;344:469-70.
2. Hach-Wunderle V, Kainer K, Salzmann G, Muller-Berghaus G, Potzsch B. Heparin-related thrombosis despite normal platelet counts in vascular surgery. *Am J Surg* 1997;173:117-9.
3. Phelan BK. Heparin-associated thrombosis without thrombocytopenia. *Ann Intern Med* 1983;99:637-8.
4. Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE, Eichler P. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. *Thromb Haemost* 2005;94:132-5.
5. Wallis DE, Workman DL, Lewis BE, Steen L, Pifarre R, Moran JF. Failure of early heparin cessation as treatment for heparin-induced thrombocytopenia. *Am J Med* 1999;106:629-35.
6. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. *Am J Med* 1996;101:502-7.
7. Lichtman MA, Williams WJ. *Williams hematology*. 7th ed. New York: McGraw-Hill, Medical Pub. Division; 2006.
8. Jang IK, Hursting MJ. When heparins promote thrombosis: review of heparin-induced thrombocytopenia. *Circulation* 2005;111:2671-83.
9. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:311S-37S.
10. Warkentin TE, Sheppard JA, Horsecwood P, Simpson PJ, Moore JC, Kelton JG. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood* 2000;96:1703-8.
11. Baroletti SA, Goldhaber SZ. Heparin-induced thrombocytopenia. *Circulation* 2006;114:e355-6.
12. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood* 2005;106:2710-5.
13. Pouplard C, Amiral J, Borg JY, Laporte-Simitsidis S, Delahousse B, Gruel Y. Decision analysis for use of platelet aggregation test, carbon 14-serotonin release assay, and heparin-platelet factor 4 enzyme-linked immunosorbent assay for diagnosis of heparin-induced thrombocytopenia. *Am J Clin Pathol* 1999;111:700-6.
14. Warkentin TE, Sheppard JA, Moore JC, Moore KM, Sigouin CS, Kelton JG. Laboratory testing for the antibodies that cause heparin-induced thrombocytopenia: how much class do we need? *J Lab Clin Med* 2005;146:341-6.
15. Juhl D, Eichler P, Lubenow N, Strobel U, Wessel A, Greinacher A. Incidence and clinical significance of anti-PF4/heparin antibodies of the IgG, IgM, and IgA class in 755 consecutive patient samples referred for diagnostic testing for heparin-induced thrombocytopenia. *Eur J Haematol* 2006;76:420-6.
16. Srinivasan AF, Rice L, Bartholomew JR, et al. Warfarin-induced skin necrosis and venous limb gangrene in the setting of heparin-induced thrombocytopenia. *Arch Intern Med* 2004;164:66-70.
17. Warkentin TE, Elavathil LJ, Hayward CP, Johnston MA, Russett JI, Kelton JG. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann Intern Med* 1997;127:804-12.
18. Swan SK, Hursting MJ. The pharmacokinetics and pharmacodynamics of argatroban: effects of age, gender, and hepatic or renal dysfunction. *Pharmacotherapy* 2000;20:318-29.
19. Clarke RJ, Mayo G, FitzGerald GA, Fitzgerald DJ. Combined administration of aspirin and a specific thrombin inhibitor in man. *Circulation* 1991;83:1510-8.
20. Walenga JM, Ahmad S, Hoppensteadt D, Iqbal O, Hursting MJ, Lewis BE. Argatroban therapy does not generate antibodies that alter its anticoagulant activity in patients with heparin-induced thrombocytopenia. *Thromb Res* 2002;105:401-5.
21. Lubenow N, Eichler P, Lietz T, Farner B, Greinacher A. Lepirudin for prophylaxis of thrombosis in patients with acute isolated heparin-induced thrombocytopenia: an analysis of 3 prospective studies. *Blood* 2004;104:3072-7.

**Author Information**

**Irfan Ahmed, MD,MRCPI**

Department of Internal Medicine, Abington Memorial Hospital

**Mary Naglak, PhD., R.D.**

Department of Internal Medicine, Abington Memorial Hospital

**Huma Rashid, M.D.**

Department of Internal Medicine, Abington Memorial Hospital