A Case Report of Hematuria in Heparin-Induced Thrombocytopenia: An Unusual Presentation Leading to End Organ Damage

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Introduction

Heparin is commonly used in many clinical scenarios, including venous thromboembolism, acute coronary syndromes, atrial fibrillation, orthopedic surgeries, dialysis, during extracorporeal circulation and peripheral occlusive disease.¹ A life-threatening complication following heparin therapy is heparin-induced thrombocytopenia (HIT). Generally, there are two types of HIT. Type 1 HIT is a mild and non-immune disorder that presents early, usually in the first 48 hours after exposure to heparin. It is caused by an interaction between heparin and platelets leading to the formation of platelet aggregates.¹,² Type 2 HIT is an immune-mediated condition which occurs 4-14 days after exposure and sometimes has life-threatening complications.² HIT has many different manifestations, so it is important to be cautious in a patient who is on heparin for any reason. Here, we are reporting a case of an elderly lady presented with frank hematuria (a rare presentation) later diagnosed as HIT and ultimately had extensive renal vein thrombosis which led to end-organ damage.

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Case Presentation

A 76 years old female known case of knee osteoarthritis for the last 8 years, had bilateral knee replacement one week back due to chronic debilitating osteoarthritis. Before her surgery complete blood count was normal with platelet count 234200/µL. After surgery, the patient was started on low-molecular-weight heparin (LMWH) 5000 IU twice daily as thromboprophylaxis. The patient was borderline diabetic and her sugar levels were controlled with dietary restrictions. She presented to
our hospital with frank hematuria and mild left-sided lumbar pain. Her platelet count of 234200/μL fell to 16000/μL by the sixth postoperative day. Blood pressure was 118/69 mmHg with a pulse of 89 beats per minute. She was afebrile and was maintaining oxygen saturation of 100%. All relevant investigations were performed (Table 1).

**Table 1: Laboratory Results**

| Test                     | Result   | Normal Range          |
|--------------------------|----------|-----------------------|
| Hemoglobin               | 9.6 g/dL | 11.5-14.5 g/dL        |
| White blood cells count  | 9010 /μL | 4000-11000/μL         |
| Neutrophils              | 55%      | 50-70%                |
| Lymphocytes              | 22%      | 20-40%                |
| Monocytes                | 6%       | 2-10%                 |
| Eosinophils              | 0.0%     | 0-6%                  |
| Platelets count          | 16000 /μL| 150000-450000/μL      |
| Prothrombin time         | 14.4 seconds | 11.5-14.5 seconds |
| Activated partial        | 45.00 seconds | 30-41 seconds |
| thromboplastin time      |          |                      |
| International normalized | 1.1      | 0.9-1.3               |
| Retics %                 | 4.0%     | 0.5%-2.5%             |
| ESR                      | 79       | 0-15 mm/hour          |

Hemolysis Screen: Negative  
Autoimmune Profile: Negative  
Malignancy Screen: Negative  
Molecular Genetic Analysis for BCR-ABL p-210 expression...Negative

**Table 2: Hematology Screening**

| Test                     | Result   | Normal Range          |
|--------------------------|----------|-----------------------|
| Protein C                | 0.82     | 0.7-1.4 u/mL          |
| Anti-thrombin III (ATIII)| 0.96     | 0.80-1.20 u/mL        |
| Factor V Leiden          | 300      | 120-300 Sec           |
| APC Resistance           |          |                      |
| Plasminogen              | 0.91     | 0.75-1.4 u/mL         |
| Procalcitonin (Endocrinology) | 1.09 | ng/mL |

Heparin was stopped immediately. She was transfused with 10 units of platelets. The patient's consultant considered sepsis leading to disseminated intravascular coagulation and accelerated platelet removal from circulation. Despite more platelet transfusion, the platelet count after eight days was 30100/μL. She underwent a CT abdomen which showed left renal vein thrombosis. At this point, HIT seemed very likely so the next day treating physician ordered a heparin-platelet factor 4 enzyme-linked immunosorbent assay (ELISA) which proved strongly positive and showed 96% inhibition with heparin. On peripheral film, there were no schistocytes and all relevant investigations were done to rule out TTP/HUS which were negative. Further, CT abdomen with contrast showed left renal vein thrombosis, hepatic vein thrombosis and partial thrombosis in the portal vein (Figure 1).

**Figure 1: CT scan abdomen showing thrombus and infarction in left kidney**

The patient was started on intravenous argatroban which is a direct thrombin inhibitor and later shifted to oral rivaroxaban after 10 days. All other possibilities were ruled out. She was being monitored as an inpatient with daily INR and PT/APTT results. Hematuria and lumbar pain settled and the patient started improving clinically. Two weeks later when she was ready to be discharged from the hospital, she complained of bilateral lower limb pain. On examination, limbs were swollen and Doppler ultrasound showed echogenic thrombus in common femoral, superficial femoral and common iliac veins. Her platelet count was in the normal range at that time and there was no evidence of active thrombosis at other sites. The common femoral and iliac veins were non-compressible with no flow detected as shown on Doppler (Figure 2).
The patient was again switched to intravenous argatroban keeping in view the high risk of thrombosis in other parts of the body. The next day, after discussing with an interventional radiologist, the patient underwent inferior vena cava (IVC) filter insertion to prevent any further catastrophic event. A week later, magnetic resonance imaging (MRI) showed persistent partial occlusion of left renal vein, left-sided infarcted kidney with some viable parenchyma and interval recanalization of the right hepatic vein. Laboratory parameters showed acute kidney injury with creatinine reaching 2.1 mg/dl and later falling to 1.0 mg/dl after one week. The patient was discharged on oral rivaroxaban and advised to have a close follow-up as an outpatient.

Discussion

Heparin-induced thrombocytopenia is a paradoxical prothrombotic state leading to widespread thrombosis causing complications like pulmonary embolism, mesenteric ischemia, ischemic limb necrosis, stroke, and acute myocardial infarction. These thrombotic complications are life-threatening in about 29% of patients, and an additional 21% have to undergo limb amputations. Some of the alarming signs pointing towards HIT may include a rash at the injection site, fever associated with rigors and chills, dyspnea and chest pain. HIT should be strongly considered as a differential diagnosis in case of platelet count dropping to less than 50% of the baseline count. The main culprit in the pathophysiology of HIT is antibodies against PF4 and heparin. In a study, Rauova and colleagues claimed that heparin and PF4 form ultra-large (>670kDa) complexes which are made up of multiple PF4 tetramers and several molecules of unfractionated heparin (UFH). Interestingly the number of these complexes is way too small when factor Xa inhibitors are used instead of UFH. The antibodies bind to these complexes on the surface of platelets and induce platelet activation by cross-linking FcγIIA receptors. The activated platelets exhibit more surface expression for PF4, creating positive feedback and further release of PF4 promoting further platelet activation. Platelet activation results in the release of microparticles which are procoagulants that further cause platelet consumption. Marked release of thrombin, activation of monocytes and endothelial injury produce characteristic venous and arterial thrombosis of HIT. Thrombocytopenia in elderly patients receiving heparin has a high association with the development of thrombotic events. Women diagnosed with HIT are 1.7 times more likely to develop a thrombotic event. In a retrospective study, there were 408 patients diagnosed with HIT out of which 66% were older than 60 years. About 10% of patients needed amputation and 20% were reported to suffer from other associated morbid conditions. The ‘4T’s’ scoring system can be used as a guide to identifying patients who are at risk for developing HIT. Heparin should be immediately discontinued once HIT is suspected. Blood samples should be taken to confirm the diagnosis. HIT screening is now available in many standard laboratories. Unfractionated heparin (UFH) poses a ten-fold increased risk of causing HIT as compared to low molecular weight heparin (LMWH). A study conducted by Smythe and colleagues revealed that the incidence of HIT in patients receiving intravenous UFH for therapeutic doses was 0.76%, whereas the percentage dropped down to less than 0.1 in patients receiving subcutaneous UFH for prophylaxis. Alternative anticoagulation in the form of argatroban, lepirudin, danaparoid, and rivaroxaban can be used. The duration of the treatment with new agents mentioned is not well-defined. However, it should be continued for 2-3 months to prevent recurrent thrombosis. These drugs are direct inhibitors of thrombin and/or factor Xa inhibitors. They also inhibit thrombin-induced reactions, including fibrin formation, activation of various coagulation factors and platelet aggregation. Its use should be regularly monitored with the activated partial thromboplastin time (aPTT) or activated clotting time (at higher levels
of anticoagulation) for argatroban, ecarin clotting time (ECT) for lepirudin, and anti-Xa assays for danaparoid. The use of warfarin is not advised until platelet count has fully recovered. Prophylactic platelet transfusion is not recommended as well as it can exacerbate the hypercoagulable state leading to additional thrombosis. Sometimes, the benefit of antithrombotic drugs is partially offset by hemorrhagic complications. The estimated incidence of major bleeding is higher with lepirudin (13-19%) than argatroban (6-7%).

## Conclusion

This case report highlights the significance of early diagnosis and prompt management of HIT as a late diagnosis can lead to disastrous complications. The prolonged use of heparin for postoperative thromboprophylaxis carries the highest risk of HIT. However, HIT can even develop with minimal heparin exposure via intravascular flushes used to maintain the patency of indwelling arterial or venous catheters. Use of LMWH or factor Xa inhibitors may be recommended for thromboprophylaxis instead of unfractionated heparin where applicable. Bleeding is uncommon in HIT but still can be a presentation. New refined drugs like danaparoid, argatroban, lepirudin, and rivaroxaban can be used for anticoagulation in patients with HIT and have shown promising results.

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