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CASE REPORT

Forgotten Source of Heparin as a Cause of Worsening Platelet Count in a Pre-Existing Heparin Induced Thrombocytopenia

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Abstract

Heparin induced thrombocytopenia is a known complication of using heparin. In this case, the patient developed deep vein thrombosis while he was in the ICU. Upon administration of heparin, he developed thrombocytopenia. After stopping heparin and using alternative anticoagulation, there was no improvement in the platelet count, however. Eventually, there was another source of heparin that could contribute to the worsening of platelet function.

Keywords: Heparin; Platelet count; Thrombocytopenia

Case Report

A 44 year old man, known for testicular cancer diagnosed in November 2004 and for which he received six courses of Bleomycin and Cisplatin from January/2005 to Febreuary/2005 had an ICU admission on 11th of March, 2005 because of the lung injury induced by Bleomycin. The patient was treated with antibiotics and steroids and was sent home on 24th of March, 2005.

The patient was readmitted to the ICU on 29th of March, 2005 because of progressive shortness of breath, productive cough, low grade fever, and right-sided pleuretic chest pain for which intubation and mechanical ventilation were required. Antibiotics including Ticarcillin, Azithromycin and Septra, and steroids were administered. Ticarcillin and septra were stopped the next day after the admission and Meropenem was started.

Blood test results on admission were as follows: WBC 26.1 10'9/L, Hb 141 g/L, Platelet count 251 10'9/L, Neutrophils count 24.9 10'9/L, INR 1.1, PTT 29.7, and PT 14.4. All the initial cultures were negative. DIC work up was negative. The patient was put on prophylactic subcutaneous heparin to prevent deep vein thrombosis.

On 1st of April, 2005, bilateral leg swelling was noticed and leg Doppler's showed bilateral lower limb deep vein thrombosis right above the knee DVT, and left below the knee DVT. Initially, unfractionated heparin was started for the patient according to the intensive care unit protocol. Due to renal dysfunction, the hematologist was reluctant to start low molecular weight heparin. The patient's platelet count dropped to 70 10'9/L, HIT assay was sent, and argatroban was started instead of heparin. HIT assay came back negative, argatroban was stopped and heparin drip was restarted.

The patient's condition was not improving, so there was a need for high FiO2. Bronchoscopy was done. All the cultures from BAL were negative except for Candida albican. Then, Fluconazole was started on 6th of April, 2005. His condition continued to deteriorate and the platelet count was declining;still requiring high FiO2 and lasix from time to time for clinical evidence of fluid overload. He still had fever.

On 11th of April, 2005, heparin was stopped because of frank blood from his mouth;no obvious source of bleeding could be identified. His Hb dropped to 80 g/L from usual 100-110 g/L and the platelet count was 80 10'9/L. His condition was unstable, not being able to undergo any upper GI endoscopy. Heparin was restarted on 14th of April, 2005. The patient's platelet count continued to drop further;

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on 17th of April, 2005, his platelet count reached 36 10'9/L. Hit assay, DIC work up were sent. Hit assay came back positive on 19th of April, 2005 (HEP.PLT.FACT.4 67%). Heparin was stopped and argatroban was started. Despite starting argatroban, the platelet count did not improve. DIC work up and all the cultures were negative. Swan Ganz was inserted on 24th of April to check the patient's fluid status. A hematologist evaluated the patient and due to the possible immune thrombocytopenia, steroids were administered. Despite all these measures, the platelet count continued to fall. The blood sample was sent for cultures. The blood culture, urine culture, and DIC work up were negative. All possible drugs suspect of causing thrombocytopenia were stopped. Blood smear showed no fragmentation and no spherocytes, and large platelets were seen.

On April 29, it was noticed that the swan ganz was heparin coated, so it was discontinued. The platelet count was 18 10'9/L. Despite all the measures taken, the patient continued to weaken and died on April 30.

Discussion

Thrombocytopenia can be caused by different etiologies including drugs such as NSAIDS and heparin. Heparin is administered to almost all patients during acute coronary syndrome, cardiac catheterization, cardiopulmonary bypass, deep vein thrombosis, and pulmonary embolism. Despite its benefits, it has many side-effects such as bleeding and thrombocytopenia. Thrombocytopenia is a well known complication of heparin therapy, usually occurring within 4 to 10 days after heparin treatment has started.[1] There are two types of heparin induced thrombocytopenia. Type I is typically characterized by a lesser fall in the platelet count, being of no clinical significance, and is due to the direct effect of heparin on platelet activation.[2]

Type II heparin induced thrombocytopenia is an immune mediated disorder which is associated with the formation of antibodies against the heparin-platelet factor 4 complex, and is a more serious form.[1]

HIT occurs in 3% of patients receiving intravenous unfractionated heparin for treatment of deep vein thrombosis or pulmonary embolism.[3]

Prophylactic subcutaneous doses of heparin, flushes to maintain arterial catheter patent and heparin coated vascular catheter produces HIT in 0.5% of patients.[4] HIT has been associated with intraperitoneal heparin exposure[5] and its postulated mechanism is absorption either via the peritoneal lymphatic system or across the peritoneal membrane.[5]

Low molecular weight heparin has lower risk of heparin induced thrombocytopenia than unfractionated heparin.[3,6] If the patient develops HIT antibody, LMWH should not be administered because of the potential cross-reactivity with HIT antibodies.[6]

Clinical manifestation of HIT usually occurs 5-10 days after initial exposure to heparin. Earlier onset of HIT is seen if the patient had been treated with heparin in the previous three or four months.[7] Thrombocytopenia due to HIT is rarely severe, usually above 20 10'9/L and therefore, spontaneous bleeding is unusual. Thrombosis is a major clinical problem associated with HIT. Thrombotic complications include new or worsening deep vein thrombosis and pulmonary emboli, arterial thrombosis of the extremities, stroke and myocardial infarction.[4]

The initial diagnosis of HIT is based on clinical suspicion. Many diagnostic tests are available including heparin-induced platelet aggregation, serotonin release assay, and solid phase immunoassay. Treatment starts with stopping any exposure to heparin and using an alternative anticoagulant. For the patients who require prolonged anticoagulation, Warfarin could be started but only if the patients with HIT are anticoagulated with thrombin-specific inhibitor, and when the platelet count has reached 100 10'9/L or more.[7]

Lepirudin and Argatroban are direct thrombin inhibitors and are used as alternative anticoagulants in HIT. Argatroban binds reversibly to thrombin active site, exerting its anticoagulant effects by inhibiting thrombin-catalyzed or induced reactions including activation of coagulation factors V, VIII, and XIII, protein C, and platelet aggregation.[8] Danaparoid is a glycoaminoglycanis approved as an alternative anticoagulant for HIT in many countries[7] but it has 10-50% in vitro cross reactivity with the HIT antibody.[6,9] Fonaparinux is not FDA approved, but some studies reported cases of successful treatment of HIT. Bivalirudin has successfully been used for patients with HIT.[1,10]

In our case, thrombocytopenia was mutlifactorial, and part of it was due to sepsis (which could be masked due to the steroids the patient was receiving), drugs (those causing thrombocytopenia were stopped eventually), and HIT (because of the use of unfractionated heparin for DVT).

It must always be kept in mind that even heparin coated catheters should be avoided in patients with heparin induced thrombocytopenia, and inserting hepa-

rin-free catheter for venous access should be done for all patients with heparin induced thrombocyopenia.

Thrombocytepenia is caused by different etiologies, including heparin. There are 2 types of heparin induced thrombocytopenia: type 1 in which thrombocytopenia is caused by the direct effect of heparin on platelet activation and type 2 which is due to the antibody formation against heparin –platelet factor 4. Physicians must keep in mind that heparin coated catheter is a source of heparin that might induce heparin induced thrombocytopenia, or it may worsen platelet counts in a pre-existing case of heparin induced thrombocytopenia.

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