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CASE REPORT

A Fatal Case of Heparin-induced Thrombocytopenia and Thrombosis

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Heparin induced thrombocytopenia (HIT) is a significant, potentially life-threatening immune-mediated adverse event that occurs several days after commencement of therapy with unfractionated or low-molecular weight heparin. We present a 51-year-old female treated with unfractionated heparin for acute deep venous thrombosis (DVT) and pulmonary embolism (PE). She developed extension of her thrombosis and was promptly diagnosed with heparin-induced thrombocytopenia and thrombosis (HITT). She did not, however, develop thrombocytopenia until 5 days after the extension of her thrombosis. The possible diagnosis of HITT is important for clinicians to keep in mind for all patients that are receiving any form of heparin, not only those patients who present with thrombocytopenia but also those with otherwise unexplainable thrombosis regardless of the platelet count. ***Journal of Hospital Medicine*** 2010;5:E14–E15. © *2010 Society of Hospital Medicine.*

KEYWORDS: heparin, thrombocytopenia, thrombosis.

Heparin induced thrombocytopenia (HIT) is a significant, potentially life-threatening immune-mediated adverse event that occurs several days after commencement of therapy with unfractionated or low-molecular weight heparin. There are several potential sequelae of HIT, the most frequent of these is thrombosis, including but not limited to deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, limb arterial occlusion, and disseminated intravascular coagulation. The prothrombotic state induced by HIT can be very significant, generating a thrombosis risk 30 times that of the general population and a mortality risk of 17% to 30% in those patients who develop thrombosis.[1,2]

Case Report

A 51-year-old female was transferred to our institution for further management of a prothrombotic state. Six days prior to transfer, she presented to an outside hospital with significant edema and discomfort of her left lower extremity. She was found to have bilateral pulmonary emboli and a left lower extremity DVT. She was anticoagulated with unfractionated heparin and transitioned to coumadin. Upon preparation for discharge she developed drastically increased edema of her left lower extremity. Coumadin was discontinued and she was transferred to our institution for alternate anticoagulation and potential interventional vascular treatments.

On examination, the patient reported pain in her legs bilaterally but was in no distress. She had marked edema of the left lower extremity with tender erythematous skin over the anterior thigh with mild cyanosis and pallor of the left toes. Pulses were not palpable but could be identified by handheld Doppler scan. Urgent bilateral lower extremity venous and arterial duplex studies were completed, revealing extensive thrombosis involving the entire deep and superficial venous system on the left and the superficial femoral, popliteal, and peroneal veins on the right.

She was treated with an argatroban drip and a complete thrombophilia evaluation commenced. The following day she was mildly obtunded and slow to mentate. A noninfused computed tomography (CT) scan of the head revealed multiple acute left middle cerebral artery ischemic infarctions (Figure 1). CT scans of the chest, abdomen, and pelvis were done to assess for further thrombosis; bilateral renal infarcts were discovered.

The hypercoagulable workup revealed prothrombin and Factor V Leiden gene mutations and anticardiolipin immunoglobulin (Ig)G, IgA and IgM that were all negative; however, heparin-dependent antibody platelet factor 4 (PF4) enzyme-linked immunosorbent assay (ELISA) was positive. Her preheparin platelet count was 149,000/μL, 185,000/μL at the time of her transfer and thrombosis extension, and 117,000/μL at its nadir, 11 days after initial heparin exposure.

Despite lower extremity thrombectomy, right common femoral endarterectomy, and therapeutic anticoagulation, the patient continued to develop massive thrombosis and she expired. The patient underwent autopsy, which confirmed her extensive thrombosis and cited multisystem organ failure as the cause of death. Additionally, this examination revealed an occult high-grade cervical cancer with lymphatic invasion.

Discussion

This case is an example of multiorgan failure as a result of the prothrombotic state induced by HIT. The thrombocytopenia of HIT is defined as either a platelet count of less than 150,000/μL or a decrease of greater than 50% from baseline.[3,4] Despite the eventual confirmation of the diagnosis by PF4 ELISA (sensitivity 80%-90%), the patient was not thrombocytopenic by definition at the time of extension of her thrombosis.[5]

Greinacher et al.[3] retrospectively evaluated 408 patients with thrombosis associated with HIT and found that at the

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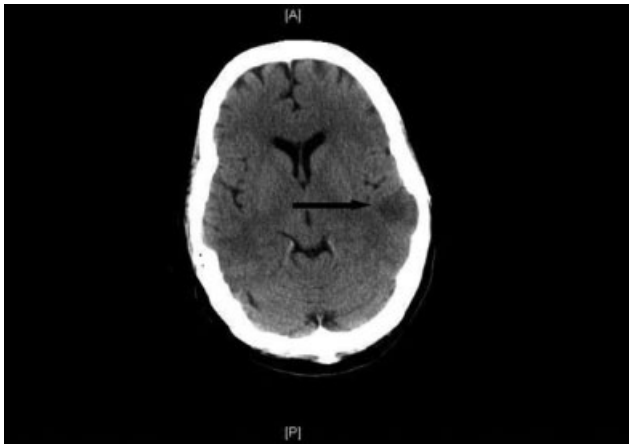

FIGURE 1. Noncontrast computed tomography scan revealing multiple acute areas of ischemia (arrow) in the distribution of the left middle cerebral artery.

time of their thrombosis 40.2% became thrombocytopenic (>50% decrease in their platelet count) 1 or more days prior to their initial thrombosis, 26% became thrombocytopenic on the day of their initial thrombosis, and 33.5% had thrombosis that preceded their thrombocytopenia with a 3-day median delay between thrombosis and thrombocytopenia. Our patient fell in the latter category, developing her thrombocytopenia 5 days after the extension of her thrombosis. The time course of this presentation places emphasis on the need for clinicians to be aware of this pattern and to have a suspicion for HIT in patients on heparin who develop thrombosis regardless of their platelet count at the time of the thrombotic event.

In addition, our patient had the occult diagnosis of cervical cancer. In a retrospective review, Opatrny and Warner[6] found that thrombotic complications associated with HIT, venous thrombosis, and PE specifically, occurred more frequently in patients with malignancy than those without malignant disease. They evaluated 64 patients with the diagnosis of HIT, made by heparin-PF4 ELISA, and discovered the incidence of thrombosis to be 73% in the patients with malignancy compared to 30% in the patients without malignancy. However, since our patient's cancer diagnosis was unknown at the time of the case events, it could not be considered.

There have been rare case reports published describing patients who develop thrombosis secondary to heparin-dependent antibodies (HDA) without meeting the above definition of thrombocytopenia in HIT. Bream-Rouwenhorst and Hobbs[7] recently reported a similar case in which a 35-year-old woman with bilateral lower extremity arterial thrombosis had additional thrombotic events after reexposure to heparin; the patient had a positive heparin-PF4 ELISA with a platelet count that remained consistently above 200,000/μL and never fell below 75% of her baseline. They cite only 22 additional cases of patients with HDA without thrombocytopenia reported in the literature since 1965 and suggest that the term "heparin-associated thrombosis without HIT" may be a more appropriate terminology to describe similar cases.

Conclusions

Early recognition and initiation of alternate anticoagulation are essential to the effective management of HIT and prevention of its sequelae. The possible diagnosis of HIT is important for clinicians to keep in mind for all patients that are receiving any form of heparin, not only those patients who present with thrombocytopenia but also those with otherwise unexplainable thrombosis regardless of the platelet count.

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