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CASE REPORT

A Case Report and Literature Review on Argatroban Refractory Heparin-Induced Thrombocytopenia

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Abstract

Heparin-induced thrombocytopenia (HIT) is characterized by low platelets and thrombosis after exposure to Heparin products. It is classically characterized by a rapid and significant drop in platelets and life-threatening thrombosis. Thrombosis can occur up to 50% of the cases if left untreated. It requires immediate discontinuation of all heparin products and switching to a non-heparin anticoagulant to prevent further thrombosis. Here we present a case of a 56-year-old male who presented to the Emergency Department with sudden onset of severe left leg pain. Duplex study showed arterial thrombosis in the common iliac and distal iliac arteries. He received TPA at once and underwent thrombectomy while his platelet continued to drop. He used Low Molecular Weight Heparin (enoxaparin) for bridging after his tonsil surgery a week prior to this hospital admission. His HIT assay was found to be positive and despite the Argatroban therapy his clinical condition continued to worsen while his platelet count continued to drop. Given the refractory nature of the thrombosis and thrombocytopenia; Intravenous immunoglobulin (IVIG) therapy was introduced. The patient showed a great response and his platelet count improved to 150,000/μ. He was discharged on warfarin with a closer follow-up. Few case reports have described the treatment of such refractory cases using intravenous immunoglobulin (IVIG), resulting in stabilized platelet counts, reduced platelet activation, and reduced thrombotic complications, the exact mechanism of which is unknown. It is thought that IVIG inhibits platelet activation by binding as platelet receptors, which would otherwise bind with heparin−platelet factor 4 complexes and HIT antibodies.

Keywords: Heparin induced thrombocytopenia, Treatment resistant heparin induced thrombocytopenia

1. Introduction

Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening disorder occurring as a complication of heparin use that is characterized by thrombocytopenia with an increased risk of thrombosis (venous, arterial, and/or microvascular). It is associated with the presence of pathognomonic platelet-activating antibodies that recognize platelet factor 4 (PF4) bound to heparin1. HIT can be divided into two types based on the pathologic response that may be immunologic or non-immunologic and severity of thrombocytopenia. HIT type I (heparin-associated thrombocytopenia) is mild and brief with transient thrombocytopenia of <100,000 that commonly returns to normal limits after discontinuation of heparin products. This non-immunologic response is brought about by an interaction between heparin and circulating platelets resulting in platelet aggregation or sequestration, often affecting up to 10% of patients within the first 48−72 h (about 3 days) of heparin use.[2] Whereas HIT type II is an immunologic response, which is associated with an increased risk of thrombosis while the characteristic onset of thrombocytopenia is 5−10 days after initiation of heparin (typical onset HIT). "Rapid-onset HIT" is a variant of HIT type II that usually results in a rapid decline in platelet counts (within 24 h) occurring in patients in whom circulating HIT antibodies are present due to recent exposure to heparin, usually within the preceding 30 days.[3−6] Treatment is immediate withdrawal of all heparin products and switching to a non-heparin anticoagulant in patients with a strong suspicion (or

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serologic confirmation) of HIT.[6,7] There have been sporadic cases in literature with severe and prolonged thrombocytopenia that show minimal or no response to standard therapy. These cases were treated with intravenous IgG (IVIg).[8–10] However, the efficacy of this treatment modality is not well studied. Here, we present a case of HIT confirmed with a serotonin release assay (SRA) that did not respond adequately to Argatroban treatment.

2. Case

This is a 56-year-old man with HIV, Squamous cell carcinoma of Tonsils, Diabetes mellitus, Avascular necrosis of the hip, deep vein thrombosis, and pulmonary embolism who was on Warfarin for anticoagulation. He underwent tonsillectomy with radical neck and lymph node dissection for the squamous cell carcinoma of the tonsils 3 weeks prior to this presentation. He was using lower molecular weight heparin and warfarin for bridging. He came to the Emergency Department with a sudden onset of severe left lower extremity pain involving his calf and thigh. Lab work at the time of admission a platelet counts of 290k/μL, PT of 16.8, INR of 1.4 and a PTT of 32.6, however his D-dimer was found to be > 20. All other labs were within normal limits. A lower extremity venous duplex was performed, which did not reveal any underlying deep vein thrombosis but showed complete arterial occlusion in the left common femoral artery extending into the left profunda femoral artery and the left proximal femoral artery, a subsequent CT angiography of the abdominal aorta with lower extremity showed pedunculated proximal and distal abdominal aorta mural thrombi (Fig. 1), proximal common iliac artery thrombosis (Fig. 2), distal left iliac artery thrombosis with presence of mural thrombi, left common femoral artery thrombosis along with left popliteal artery thrombosis. TPA was started and vascular surgery was consulted, he underwent emergent iliofemoral thrombectomy and left lower extremity fasciotomy. A follow-up CT angiography after the procedure showed markedly improved aortoiliac flow but presence of left femoral artery occlusion and a new right popliteal artery occlusion, hence he underwent bilateral lower extremity thrombectomy along with right lower extremity embolectomy. His post operative course was complicated by a low platelet count which showed a steady decline to 43k/μL on post operative day 3. A review of his chart showed that he had received Enoxaparin up to 4 days prior to his hospital admission as part of bridging therapy after neck dissection surgery raising suspicion for Heparin Induced thrombocytopenia. His 4-T score was 5 points while serotonin release assay and Elisa panel for HIT were positive, thereby confirming the diagnosis of Heparin induced thrombocytopenia.

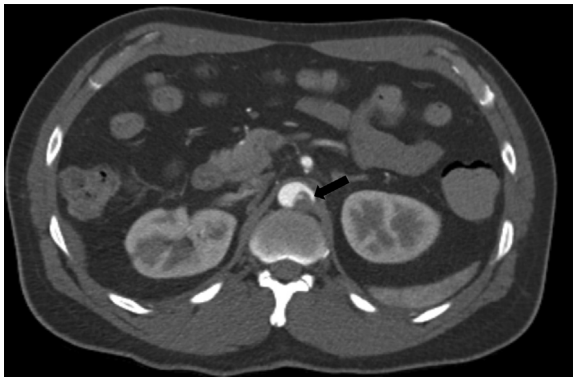

Fig. 1. CT angiogram: Irregular mural thrombus seen in distal abdominal aorta resulting in moderate luminal narrowing (Black arrow).

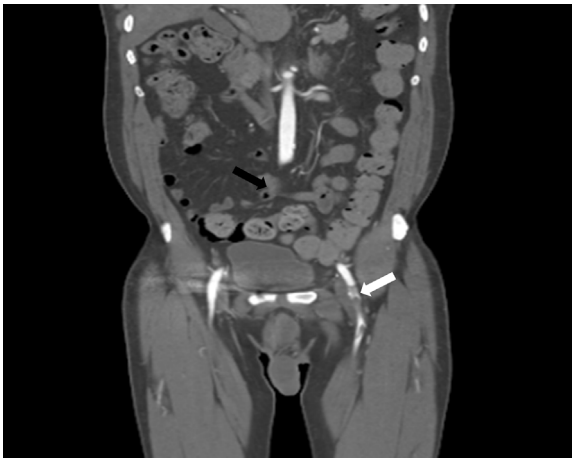

Fig. 2. CT angiogram: Distal abdominal aorta thrombus into the origin of the right proximalcommon iliac artery (black arrow), with severe luminal narrowing of left iliac artery (white arrow).

Hematology was consulted and he was started on Argatroban infusion at 1.5 mcg/kg/min. However, despite these measures his platelet counts continued to decline, with a nadir of 8k/μL >72 h after starting therapy. Given the refractory response, he was given Intravenous immunoglobulin (IVIG) at 1 ml/kg for two days along with Argatroban infusion. After the second IVIG treatment, the patient's labs showed a remarkable response and his platelet count improved to 150,000/μL. Subsequently he underwent multiple procedures during his hospitalization including fasciotomy and wound closure to salvage his Left lower extremity and was discharged from the hospital in a stable condition to acute rehab facility on coumadin with a normal platelet count.

3. Discussion

HIT occurs in 0.1–5% of patients receiving heparin while the type of heparin formulation used significantly affects rates of HIT,[11–13] with HIT less likely to occur in patients receiving LMWH compared to unfractionated heparin when used for thromboprophylaxis such as our patient.[14,15] HIT causes a potentially life-threatening hypercoagulable state with up to 50% of patients developing thromboembolic complications associated with a mortality rate of up to 30%.[12,16,17] The diagnosis of HIT usually requires a combination of both clinical features, laboratory testing with 4 T score and laboratory evaluation with heparin antibodies (PF4) and serotonin release assays (SRAs) being used. Treatment revolves around cessation of heparin products and use of alternative anticoagulation with parental direct thrombin inhibitors are used effectively to manage these cases until the platelet count rises back in approximately 3–7 days but it can take up to several weeks in refractory cases. Even with early diagnosis, HIT carries significant morbidity (7%) and mortality (1%).[18–22] It has been shown that the binding of platelet factor 4 (PF4) to heparin may lead to the formation of IgG antibodies specific to the heparin-PF4 complex. These IgG antibodies while attached to the heparin-PF4 complex, bind to the FC receptor on the platelet surface causing widespread platelet activation resulting in a release of pro-thrombotic substances (such as thrombin) leading to hypercoagulability.[23] The use of IVIG was first published by Frame and colleagues in 1990 describing a 62-year-old woman with severe HIT complicated by venous thromboembolism with excellent response seen on day 3 of high-dose IVIG treatment.[8] Greinacher et al. were the first to evaluate the role of IVIg by describing the competitive inhibition of platelet receptor (FcγRIIa) mediated thrombosis by higher levels of plasma IgG. Though later Padmanabhan et al. describe the mechanism of action of IVIg therapy in severe thromboembolism and prolonged thrombocytopenia refractory to standard treatment. They concluded that there may be certain platelet receptor (FcγRIIa) genotypes (HH, HR, and RR131) that are resistant to standard therapy and have shown a good response to IVIg treatment both in vivo and in vitro.[9,10] Our patient had been exposed to enoxaparin after the vascular procedure during bridging therapy. Rarely, cases of HIT are severe and treatment-refractory. Unfortunately, the incidence or prevalence of such cases is unknown. Our patient had severe HIT that was refractory to standard therapy, yet he showed rapid and sustained improvement following IVIG treatment. HIT continues to cause morbidity and mortality in hospitalized patients. Findings seen in our patient after treatment show that the use of IVIg in patients that are refractory to standard therapy deserves a careful prospective study. Since IVIg treatment itself may predispose to thromboembolism, treatment decisions should be made cautiously after individual risk-benefit assessment.

Conflict of interest

There is no conflict of interest.

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