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Heparin induced thrombocytopenia - A case report

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Abstract

Heparin induced thrombocytopenia, is a dreaded complication, of heparin administration. It often presents with a drop in platelets, the more serious type, type-2 also includes thrombosis, which is why Heparin induced thrombocytopenia is a worrisome complication of heparin. Though it can occur with both types of heparin, Unfractionated and low molecular weight heparin, it is more common with unfractionated heparin use.

Description

This is a case report about a 42 year old male, of Asian ethnicity, without any significant PMH developed a pulmonary thrombus, which presented 30 hrs after he took an 8 hour flight. He wasn't dehydrated, was not on any medication, and did not suffer any injury. 30 hours after landing, he developed severe shortness of breath. He arrived to the ED, 5 hours after developing SOB; his RR was 20/min. His serum electrolytes were serum sodium of 132 mmol/L, potassium of 3.6 mmol/L, chloride of 104 mmol/L, bicarbonate of 22 mmol/L, BUN of 15 mg/dL, creatinine of 1.0 mg/dL and glucose of 92 mg/dL. Her Leukocyte count was 10.0 x10^3 per µL, hemoglobin was 13.1 g/dL, and platelet count was 170 x10^3 per µL. Arterial blood gas sampling showed a pH of 7.48, $PaCO_2$ of 33 mmHg, PaO_2 of 70mmHg, and 92% and FiO_2 of 21%, with a normal D-dimer level. As his blood pressure, systolic was 90 mmHg and his HR was 113/min, was stated on intravenous fluids, vasopressors. Many differential diagnoses such as angina, pneumothorax were rejected due to normal ECGs, normal echocardiography and an unremarkable chest X-ray. A diagnosis of pulmonary thrombo-embolism by exclusion was considered. Empiric anticoagulation with unfractionated heparin was sought. Even though his wells criteria [1] of 4.5 points put him into a low probability of PE, anticoagulation was started and a HRCT was ordered, which showed, a filling defect in a sub-segmental pulmonary vasculature, which became evident after contrast enhancement. Thus a diagnosis of pulmonary thrombo-embolism was made.

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A week after he presented, his laboratory results showed a distinctive drop in platelets count, from the normal range, a week ago it dropped down to 52,000/ micro L and soon after he started experiencing right calf pain, on a Doppler US of the right calf, he was found to have a 2.2 cm long, deep vein thrombus. It remains unknown that if he developed the DVT in his calf, along with the PTE or if it was due to heparin, due to a syndrome called heparin induced thrombocytopenia, (HIT). On suspecting HIT, heparin was immediately stopped, and direct oral anticoagulants were started- abixaban, a factor X a inhibitor, for 6 months in lieu of symptomatic pulmonary embolism, and heparin induced thrombocytopenia with thrombosis. He was scheduled for routine follow-ups, for early detection of a recurrent PTE, monitor resolution of his thrombocytopenia and DVT.

Discussion

Heparin induced thrombocytopenia, is a serious complication of heparin administration, that includes disastrous complications like arterial and venous embolisms, skin necrosis, limb and organ ischemia, apart from low platelet counts. Though heparin is a very common anticoagulant, this complication only occurs in a very small subset of patients, irrespective of the dose of administration of heparin. Structurally, heparin consists of alternating glucosamine and uronic acid elements, and its anticoagulant effect is due to heparin pentasaccharide, which has a high affinity in binding and inactivating ATIII (antithrombin III). Actually this effect is mediated by heparins binding to AT II (antihrombin- II), which produces a marked structural change in ATIII, and thus heparin inactivated coagulation factors, IIa, Xa and IX a, and thus prevents conversion of fibrinogen to fibrin [2]. Heparin is also present in our body, in the mast cells as granules, of the liver lung and intestines. Main issues with heparin administration are, increase in clotting time, amongst others such as osteoporosis and hyperaldosteronism after long term use. The bleeding with heparin, is very severe, and potentially disastrous, but its effects can be rapidly reversed with protamine sulphate, its antidote Low molecular weight heparin (LMWH), include enoxaparin, dalteparin, and tinzaparin. Like Unfractionated heparin (UFH), the Low molecular weight heparins (LMWH) inhibit both factors Xa and IIa, but the synthetic heparin, fondaparinux inhibits only factor Xa. Though there is no antidote for LMWH overdose, 60% of the anticoagulant effect of LMWH can also be neutralized by protamine sulphate [3].

UFH, can be monitored using assays, such as the (activated) partial thromboplastin time- aPTT, but since LMWH mainly inhibits factor X a, aPTT cannot be used for it quantification. Another point of difference between unfractionated and Low Molecular Weight heparin is the considerable difference in size, while heparin has about 15000 units, LMWH, which is a desaturated, condensed heparin, has about 4000 units. One the major side effects, using any kinds of anticoagulant, is bleeding, though the risk depends on co morbid conditions, disease process, baseline value of coagulation factors, renal creatinine clearance, use of other drugs such as other anticoagulants or NSAIDs. Other side effects include, skin necrosis, osteoporosis, hyperkalemia, systemic anaphylaxis, and the topic of our case discussion, Heparin induced thrombocytopenia. Even after multiple adverse effects, the reason why heparin is used is due to its quick onset of action, its use particularly in individuals with reduced renal clearance, ability to monitor the activity by using aPTT, and availability of an antidote when toxicity occurs. Heparin induced thrombocytopenia, is an unforeseeable complication of heparin use, though it can occur with both UFH and LMWH, its presentation is common with UFH. There are two kinds of Heparin.

Type-1 Heparin induced thrombocytopenia occurs mainly due to non-immune platelet aggregation, resulting in transient drop of platelets, after about 2 days of starting Heparin treatment, with this type of Heparin induced thrombocytopenia (HIT), there is no requirement to reduce or discontinue the heparin, platelet no, reaches about 100,000/microL. The type 2 of HIT, which is more serious, has a myriad of symptoms to its name. The platelet count drops to an average of 60,000/microL, and this condition, uniquely causes patients to develop, thrombosis, which can be arterial or venous in nature, more commonly in the arm, or VTE and PE, that is why this condition is often called HITT- heparin associated thrombocytopenia and thrombosis, the reason behind it being, after administration of heparin, a protein called PF 4, present in the platelets in granule form, - alpha granules, bonds to heparin. This heparin-PF4 complex forms a neoantigen, results in formation of antibodies, which bind to this complex, leading to continued platelet activation which leads to more and more PF 4 release, thus creating a cycle. Now this platelet activation, result in consumption of platelets causing thrombocytopenia, and also, a state of thrombosis. The antibodies formed in HIT, are primarily of type IgG, though some IgM antibodies are formed, the heparin-PF4 complex, stimulates release of IgG antibodies, within days [4]. The typical onset of thrombocytopenia occurs 5 to 10 days after the initiation of heparin therapy. This time period is supported by studies showing that heparin-dependent antibodies usually develop between five and eight days after heparin exposure [5]. Since, formation of heparin dependant antibodies against heprin-PF4 complex, develop about after at least 4 days of heparin exposure [6]. Typically the thrombocytopenia in HIT occurs in the first 5-19 days of heparin use. Early onset does occur, if patients have been exposed to heparin in the past 3-4 months [7]. Thrombosis which occurs in HITT, not only causes VTE and PE, but also, skin necrosis which may o may not be at the site of heparin injections, but the most common area is abdomen, organ infarction and limb gangrene.HIT-2 is suspected if we find any of the following, especially with preceding heparin use in the past week [8]:

- New onset fall in platelets
- Fall in platelet count by 50 percent or more, even if the platelet count exceeds 150,000/microL
- Thrombosis, which can be arterial or venous in nature
- Sites of skin necrosis
- Acute reactions which may include fever, tachycardia, hypertension, SOB, cardiopulmonary arrest, or anaphylaxis reaction after intravenous heparin

It is important, that we don't wait for thrombosis to develop or for detection of the antibodies against heparin-PF4 neoantigen, for the diagnosis of HIT-2, as early timely intervention is necessary, for a better prognosis, and reduced morbidity. Though HIT type 2 is usually diagnosed based of clinical features, and labs such as fall in platelets, it can be confirms by detecting the antibodies. The antibody detection, are of 2 types, an immunoassay, which simply detects the presence of these antibodies, which may be present in HIT, but also in cases such as lupus. There is another type of assay called the functional assay which detects the ability of these antibodies to bind to the PF4

heparin complex and initiate HIT-2. This assay, doe take time to come in, which is why, it cannot be used to decide whether the diagnosis [9]. Other tests, which can confirm Heparin induced thrombocytopenia, type 2 (HIT 2) include- serotonin release assay and measuring heparin induced platelet activation. On suspicion of HIT type 2, all heparin, including heparin bridges to warfarin must be discontinued, and other heparin independent anticoagulation should be initiated like direct oral anticoagulants. This will ensure no further platelet activation, and will prevent thrombosis. The heparin independent anticoagulants, include, direct thrombin inhibitors like bivalrudin and direct oral anticoagulants, which inhibit factor Xa. It has to be made sure that the patient does not develop thrombosis, particularly DVT, even if patients have low probability or are asymptomatic, they should still be screened for a DVT [10].

Conclusion

This particular patient highlights the need for a quick diagnosis of heparin induced thrombocytopenia, type II, even at the slightest suspicion, and that diagnosis, should be made before confirmatory tests, in order to prevent the dreaded complication- thrombosis. Once the diagnosis is made, it s imperative that heparin, and all other heparin dependant medications like warfarin be discontinued to reduce the risk of thrombosis, and to initiate immediate heparin independent anticoagulation. Also it is important that thrombosis should be screened for, as it can show up even without symptoms, and therefore Heparin induced thrombocytopenia is an unforeseeable complication.

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