

Heparin Induced Thrombocytopenia in a patient with Antiphospholipid Syndrome

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Abstract

Heparin-induced thrombocytopenia (HIT) is a less commonly encountered adverse reaction of heparin characterized by formation of heparin complex with platelet factor 4 due to formation of autoantibody. HIT is reported in about 2% of all patients receiving heparin, out of which 35% develop thrombosis. In Antiphospholipid syndrome autoantibodies are generated to phospholipid binding proteins which are risk factors for thrombosis and pregnancy complications. In this report we present case of a patient with recurrent venous thromboembolism receiving heparin and was found to develop HIT with coexistence of Antiphospholipid syndrome.

Keywords: Deep Vein Thrombosis (DVT); Pulmonary Embolism (PE); Antiphospholipid Syndrome (APS)

Introduction

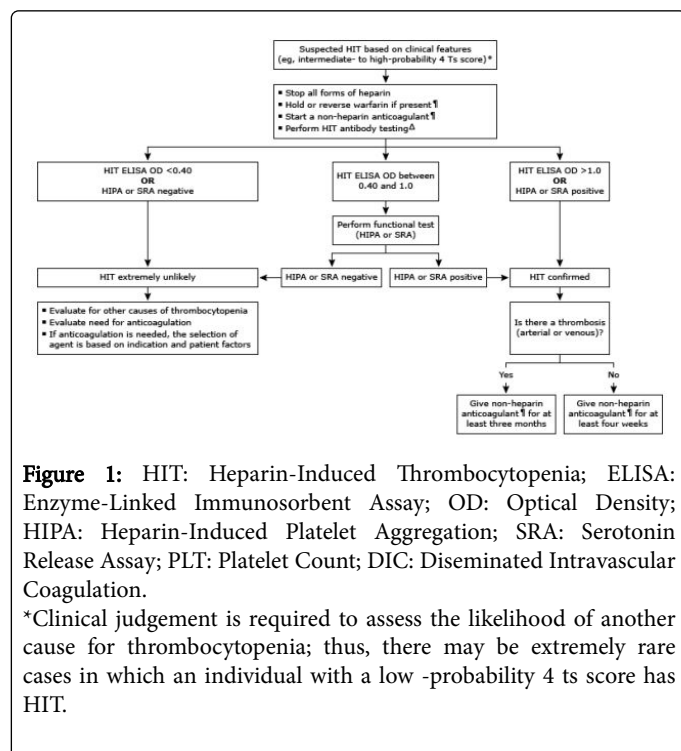
A 30-year-old female with history of recurrent episodes of deep venous thrombosis and pulmonary embolism presented with painful left lower extremity swelling. She was receiving low molecular heparin at the time of presentation. Physical examination of the affected lower limb showed a swollen, mildly tender, and warm whole left lower limb. There was mild tachycardia and tachypnea as well. [1-4]. Lower extremity doppler ultrasonography revealed an occlusive venous thrombosis (DVT) extending to calf veins from femoral veins. There was previous history of repeated hospital admissions for deep vein thrombosis and pulmonary embolism. Patient previously received low molecular weight heparin and direct oral anticoagulants with partial improvement [5-7]. A high resolution computed tomography of the chest with contrast showed embolus in subsegmental branches of right pulmonary artery. Patient was receiving low molecular weight heparin, which was withheld and intravenous heparin was started. While receiving unfractionated heparin, full blood counts were done which revealed reduction of platelet counts to 30000/ μ L on 5th day with initial platelet count of 200000/ μ L. Patient developed right-sided pleuritic chest pain. There was extension of deep vein thrombosis in lower limb up to left internal iliac vein. Pretest probability revealed a score of 5

which accounts for intermediate probability of heparin induced thrombocytopenia (HIT). Heparin was stopped, and due to non-availability of Enzyme-linked immunosorbent assays (ELISA) for heparin induced thrombocytopenia, patient was started on alternate anticoagulant i.e. fondaparinux 7.5 mg subcutaneously and monitoring with serial venous duplex ultrasound was continued. Due to non-availability of FDA approved medicines for heparin induced thrombocytopenia (HIT) like argatroban and danaproid, we chose fondaparinux. Continuous oxygen inhalation was given throughout. Three days after starting fondaparinux, partial recanalization of lower limb deep vein thrombosis within the left external iliac vein and the left femoral popliteal system was clearly demonstrated. After 10 days of starting fondaparinux, the platelet count rose up to 100 \times 10⁹/L and she was maintaining her oxygen saturation at 97% with 2 L/min. Antiphospholipid antibody profile demonstrated elevated anti- β 2 glycoprotein 1 and anticardiolipin. Once platelet count improved and DVT recanalization was achieved, warfarin was started (Figure 1 and Table 1). Warfarin was overlapped with fondaparinux for 4 days after INR reached 2.5. Three months after the initial diagnosis, antiphospholipid antibodies levels were still elevated, confirming the diagnosis of antiphospholipid syndrome (APS). Patient had no history of miscarriage or recurrent pregnancy loss. She had one alive issue. We discussed about pregnancy complication with patient and avoiding heparin during pregnancy and the risk of foetal toxicity with warfarin. Patient decided to avoid pregnancy in future [8,9].

4 Ts score parameters	
Thrombocytopenia	
PLT decrease >50% AND nadir \geq 20,000/ μ L AND no surgery within preceding 3 days	2 points
PLT decrease >50% BUT surgery within preceding 3 days and nadir that does not fit criteria for 2 or 0 points (eg, 30 to 50% fall or nadir 10,000 to 19,000/ μ L)	1 point
PLT decrease <30% OR nadir <10,000/ μ L	0 points
Timing of onset after heparin exposure:	
5 to 10 days OR 1 day if exposure within past 5 to 30 days	2 points

Probable 5 to 10 days (eg, missing PLT counts) OR >10 days OR <1 day if exposure within past 31 to 100 days	1 point
≤4 days without exposure within past 100 days	0 points
Thrombosis or other clinical sequelae:	
Confirmed new thrombosis, skin necrosis, anaphylactoid reaction, or adrenal haemorrhage	2 points
Suspected, progressive or recurrent thrombosis, skin erythema	1 point
None	0 points
Other cause for thrombocytopenia	
None	2 points
Possible (eg, sepsis)	1 point
Probable (eg, DIC, medication, within 72 hours of surgery)	0 points
Interpretation:	
0 to 3-Low probability	
4 to 5-Intermediate probability	
6 to 8-High probability	
For patients receiving warfarin who do not have a thrombosis, warfarin should be withheld until stable anticoagulation has been achieved; for those with HIT who have a thrombosis while receiving warfarin, the warfarin should be reversed with vitamin K and held until stable coagulation has been achieved. Options for anticoagulation in HIT include argatroban, bivalirudin, danaparoid, fondaparinux, or a direct oral anticoagulant (dabigatran, apixaban, rivaroxaban, edoxaban). Refer to the up to date table on selection of non-heparin anticoagulants in HIT for important considerations related to administration route, half-life, use in renal and hepatic failure, and monitoring. Warfarin can be used after the appropriate duration of initial anticoagulation, anticoagulation as it is expected to resolve rapidly upon heparin discontinuation. The specific testing needed depends on availability and turnaround time of an ELISA-type immunoassay and a gold standard test (HIPA or SRA). Refer to up to date for the optimal sequence and interpretation of testing. If the ELISA result is between 0.40 and 1.00, a gold standard test should be performed	

Table 1: 4 Ts score parameters.



Discussion

Usually antiphospholipid syndrome and heparin-induced thrombocytopenia don't coexist. There is no such case reported from our country previously. Another feature is a unique presentation as this patient received low molecular weight heparin off and on previously during hospitalization as well but developed HIT on receiving unfractionated heparin.

A similar case was reported by Tun et al. in which a 42-year-old female developed pulmonary embolism, superior mesenteric artery thrombosis, and had thrombocytopenia and positive HIPA. However, serotonin release assay was not reported [10].

Another study also suggests that APS may increase predisposition to HIT [11].

A retrospective study reported that out of 20 patients with primary APS, 7 developed HIPA. 2 of the 7 patients had positive aggregation tests for HIT [12]. Another study proposed that, the vascular endothelium seen in APS leads to exposure of glycosaminoglycans such as heparin sulphate that may complex with platelet factor 4. This may cause molecular modification that produces neoantigens and HIPA [13-15]

Similarly, there are two other reported cases of HIT in patients with APS who had thrombosis but negative HIPA. So, presence of APS antibodies may interfere with HIT diagnostic tests [16,17]

In a patient with both HIT and APS, the 14th international congress on APS task force suggests anticoagulation with argatroban or

danaparoid. The use of danaparoid has been discontinued in the United States. There are four other case reports in the literature, detailing the successful use of fondaparinux in patients with concurrent APS and HIT. Our case further favors use fondaparinux in venous thromboembolism with HIT and APS [18-20]

There is genetic predisposition for formation of HIT antibody in patients having prothrombin G20210 A polymorphism 20.

Conclusion

In patients with APS, thrombocytopenia developed or increased during heparin therapy should be investigated for HIT antibody. Timely diagnosis and prompt treatment can prevent morbidity and mortality. It is also suggested that in this era of modern medicine, the multidisciplinary approach to diagnose HIT must be appreciated.

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