Heparin-induced Thrombocytopenia with Normal Platelet Count: A Cautionary Tale of Delayed Diagnosis

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Key Clinical Message:

HIT can present without thrombocytopenia and with a low pretest probability, leading to delayed testing and treatment. Clinical judgment and diagnostic tools are crucial for timely detection and treatment of Heparin-induced thrombocytopenia (HIT).

Introduction

Heparin, also known as unfractionated heparin (UFH), is a widely used anticoagulant in medicine due to its pharmacological properties, such as the rapid mechanism of action, simplicity of monitoring, and rapid reversibility (1). Therefore, heparin remains ahead of other anticoagulants in many circumstances, such as cardiac surgery and mechanical valves, where alternatives are limited. But unfortunately, along with its beneficial properties, it can lead to severe adverse effects such as Heparin-induced thrombocytopenia (HIT). (2,3)

HIT is a severe and potentially fatal prothrombotic syndrome. (4,5) Additionally, HIT frequently goes undiagnosed since thrombocytopenia is common in hospitalized patients and can be brought on by various causes. HIT refers to a platelet count drop within 5-10 days of receiving heparin. There are two distinct forms of HIT. The first type (HIT type 1) is benign without an elevated risk of thrombosis; it was once known as heparin-associated thrombocytopenia. The second form is type 2, which usually occurs due to an immunological reaction to heparin-platelet factor 4 antibody complexes (2,6). The reaction results in platelet activation, the release of procoagulant platelet microparticles, increased thrombin release, platelet consumption, and thrombocytopenia. Therefore, thrombosis is a much more common sign of HIT than bleeding (5,7).

Current guidelines recommend using the 4T pretest probability scoring system (Table 1) if HIT is suspected. This is then used to guide testing and treatment. If the score is intermediate to high, PF4 testing is performed. If positive, the diagnosis is confirmed through an ELISA test or serotonin release assay (SRA). If the PF4 is negative, HIT is ruled out. When the diagnosis of HIT is intermediate or high in probability and leads to serological testing, all forms of heparin should be discontinued (8,9,10). However, anticoagulation can be continued with non-heparin anticoagulation, such as danaparoid, lepirudin, or argatroban. (10,11)

A low score on the 4T would result in a $< 1\%$ pretest probability. In this case, further testing is not recommended in most cases. This has led to an absolute reliance on the 4Ts to guard against PF4 testing in several hospital settings. In some circumstances, the provider must input patient data and obtain the score before being allowed to test.

Are guidelines infallible or absolute? What happens when Physicians are guided to rely solely on policies and forget about their clinical judgment?

In this article, we report an interesting case of HIT thrombosis without thrombocytopenia, and with a low pretest probability that led to delayed testing and treatment. We aim to raise awareness of not relying blindly on guidelines but using them and therapeutic guides and tools to aid in our clinical diagnosis and treatment of patients.

Case

The patient was a 40-year-old African American male who presented to the emergency department (ED) for dyspnea. His medical history was significant for coronary artery disease, heart failure with preserved ejection fraction, OSA, hypertension, and medical non-compliance. Social history was significant for alcohol, tobacco, and marijuana use. Family history was significant for an unspecified clotting disorder.

On arrival at the emergency department, the patient was obtunded and lethargic. Vital signs were significant for a heart rate (HR) of 103, blood pressure (BP) of 192/121 mmHg, respiratory rate (RR) of 26, and oxygen saturation of 87% on room air. Physical exam was notable for morbid obesity, diminished breath sounds bilaterally, and 1+ bilateral pitting edema.

Initial serology was notable for hemoglobin of 17.9, hematocrit of 58.7, platelets of 248, and normal renal function based on BUN/Cr. Venous blood gas revealed a respiratory acidosis with a pH of 7.3 and PCO2 of 72.7. Chest x-ray did not reveal an acute cardiopulmonary process. With his hypercapnia and inability to protect his airway, he was intubated and transferred to the intensive care unit. In addition, DVT prophylaxis heparin Subcutaneous was started on day two of admission.

Treatment was started for heart failure exacerbation with intermittent IV diuretics, and therapy was later escalated to continuous infusion due to poor initial response. However, the patient eventually responded to treatment and began to have significant diuresis. Initially, his renal function improved but plateaued and then worsened, prompting a Nephrology consult.

On hospital day seven, a palpable cord was noted along the medial aspect of the left arm. Bilateral upper extremity duplex revealed occlusions of the left brachial, radial, and ulnar arteries (Image 2). The patient's prophylactic dose of heparin was increased to the therapeutic dose.

The renal injury worsened, and he developed oliguria, prompting hemodialysis (HD). Unfortunately, immediately after starting HD, the HD lines began to clot. Dialysis was again attempted on a different unit with similar results. With this new event and worsening polycythemia and arterial thrombus, Hematology was consulted, and labs were ordered to evaluate possible clotting disorders. Anti-phospholipid was negative, the HIT 4T score was 1-2 with platelets remaining stable at 271 on day seven of heparin administration (Table 2), therefore a low probability.

Additionally, on day nine, the patient developed rectal bleeding. Anticoagulation was held, and CTA of the abdomen revealed no active gastrointestinal (GI) bleeding but found an acute thrombus of the left main renal artery and multiple right renal infarcts. Colonoscopy was performed, but no active bleeding was noted. Anticoagulation was restored after as bleeding was due to rectal tube injury.

With these findings, and the patient requiring mechanical ventilation, a CTA of the chest was ordered, which revealed tiny, distal, bilateral upper lobe non-occlusive pulmonary emboli. Even though thromboses were present, anticoagulation had to be held due to continued GI bleed and polycythemia developing into significant anemia.

On day 14, the patient was found to have a left dilated pupil. CT scan of the head showed large, symmetric infarcts within the occipital poles and retinal artery thrombus. With ongoing thromboses and hemorrhages, and despite no thrombocytopenia and a low 4T score ($< 1\%$) , he was started on Argatroban. Subsequently, a PD4 antibody was ordered and resulted positive; this was confirmed by Serotonin Release assay.

Discussion

The incidence of HIT is estimated to be about 0.1-5% of patients exposed to heparin. However, despite the low incidence of HIT, it is considered a life-threatening condition with high morbidity and mortality, as demonstrated by our case report (11,12). The pathogenesis of HIT has been researched in depth over the years. It results from autoantibodies IgG directed against PF4 complexes with heparin. Thrombocytopenia (Platelets <150000) with or without thrombosis is the most common feature of HIT, occurring in 90-95% of patients (10,11,13). 5-10% of patients diagnosed with HIT do not present with absolute thrombocytopenia, but have relative thrombocytopenia, which means platelet count drop between 30-50% from baseline (10).

The 4Ts Pretest probability has been widely implemented in patients with suspected HIT since 2006 to identify HIT (14,15). It is a point-based test, with points assigned for thrombocytopenia, the timing of platelet count drip, thrombosis, and other causes of thrombocytopenia. Furthermore, this test has high negative predictive values with low probability scores (9). Our patient's platelet levels fell from 241 on day one of heparin exposure to 190 on day ten. Despite this drop, levels remained above 150 and were less than a 30% drop from admission. Also, platelets count on day seven, and eight were 271,253 respectively, contradicting the pathophysiology of HIT that includes platelet consumption. With a low pretest probability with the 4Ts score and no initial clinical suspicion for HIT, testing was not indicated nor recommended (9,15,16). Hence, our patient developed multiple life-threatening thromboembolic events, including massive

occipital infractions while on heparin, and continued despite its discontinuation. The error, in this case, was to rely on the high negative predictive value and sensitivity of low 4T pretesting that could exceed 98% (9). The reliance on the pretest probability of the 4Ts also deferred the Hematology and Pharmacy teams from further investigation into HIT. The medical team did discuss testing for HIT when the anticoagulation serologies were initially sent. However, they were detracted by the specialists and pharmacists. Therefore, the discontinuation of heparin was delayed leading to more fatal thrombosis. In brief, our patient never had neither absolute nor relative thrombocytopenia, contradicting current guidelines for HIT.

To our knowledge, limited studies have investigated the occurrence of HIT without thrombocytopenia. Busche, Marc Nicolai, et al., published in a case report published in 2009, showed a 26-year-old in a burn ICU who developed thrombotic events after 13 days of heparin infusion without thrombocytopenia (17). Heparin was stopped, and the HFP4 test was positive, later confirmed by ELISA. This finding is consistent with our report that HIT could occur without a fall in platelet count and could be associated with major thromboembolic events. However, in this patient, thrombosis occurred after 13 days of heparin compared to our case, which occurred within 5-10 days of heparin infusion. In another case report titled "Heparin associated thrombosis without thrombocytopenia," Phelan Brian demonstrated a 64-year-old who developed a series of thromboembolic complications after the initiation of heparin drip (18). He reported that these events were associated with platelets of 187, which did not show absolute thrombocytopenia. However, the platelets baseline, in this case, was 365 before the start of the heparin drip. Hence, there was relative thrombocytopenia due to a more than 50% fall in platelet counts. This finding contradicts the case title and supports the current guidelines' definition of HIT. Moreover, Greinacher, Andreas, et al., in a retrospective analysis of 408 patients aiming to identify risk factors for developing HIT-associated thrombosis, illustrated that 4.4 % of patients diagnosed with HIT did not have thrombocytopenia. At the time of clinical diagnosis of HIT, a decrease in platelet counts of at least 50% occurred in 271/319 (84.9%) patients. Of the remaining 48 patients, HIT was suspected in 14 patients because new thrombosis without a platelet count fall greater than 30% (4.4%). (19)

Further research into current recommendations of the 4Ts mentions using the pretest probability in conjunction with clinical judgment, as clinical judgment and assessment is required for evaluating the likelihood of HIT. In addition, evidence-based algorithms describe that there may be extremely rare cases of HIT with a low pretest probability. Additionally, the 4 Ts score has yet to be validated on patients receiving prophylactic dose of heparin. However, many institutions use this score to guide testing and at times, strongly discourage testing for HIT unless the 4Ts score is intermediate or high.

Our case touches on not relying blindly on guidelines but using them as therapeutic guides and tools to aid in our clinical diagnosis and treatment of patients. As Physicians, we cannot blindly diagnose or treat diseases. As many of us were taught, diseases do not follow the textbook. Therefore, the physician must remember to trust their clinical judgment and use evidence-based medicine to guide the diagnosis and treatment. Medicine is both a science and an art, and being an artist is human.

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4 Ts score parameters:	
Thrombocytopenia:	
▪ PLT decrease >50% **AND** nadir ≥20,000/microL **AND** no surgery within preceding 3 days	2 points
▪ PLT decrease >50% **BUT** surgery within preceding 3 days **OR** any combination of PLT fall and nadir that does not fit criteria for 2 or 0 points (eg, 30 to 50% fall or nadir 10,000 to 19,000/microL)	1 point
▪ PLT decrease <30% **OR** nadir <10,000/microL	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 hemorrhage	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 points – Low probability (<1%)	
4 to 5 points – Intermediate probability (approximately 10%)	
6 to 8 points – High probability (approximately 50%)	

Date	HB	HCT	Platelet	Events
2012	17.2	52.8	240	
2017	16.7	50.3	205	
2020	17.8	55.1	257	
2021	19	59.4	239	
5/30/2022	17.9	58.7	248	ED presentation for SOB
5/31	17.6	58.5	241	MICU admission + First SC prophylaxis heparin
6/1	17.3	55.2	181	
6/2	-	-	-	
6/3	17.5	57.4	219	
6/4	17.4	58.2	218	
6/5	17.2	57.1	254	
6/6	18.3	59.5	272	Extensive UL thrombus + Heparin drip
6/7	18.8	59.1	271	Heparin switched to Enoxaparin full dose
6/8	19.8	64.1	253	Started HD for worsening kidney functions + HD lines clotted +Heparin CTPE for worsening resp status showing PE + Hematology consult GI bleed during night shift + CT GI bleed showing thrombus of left main renal artery
6/9	17.8	58.8	192	Sigmoidoscopy showing non bleeding erosions from rectum + normal EGD
6/10	13.4	44	190	
6/11	9.4	30.6	204	
6/12	9.9	32.3	272	
6/13	8.3	25.9	263	Branched retinal artery occlusion + CT head showing occipital infarct
6/14	8.2	25.6	264	PF4 positive and argatroban started + normal colonoscopy
6/17	7.9	25.1	428	Patient transferred to hospital service