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CASE REPORT

Great white sighting: a case of heparin-induced thrombosis with thrombocytosis

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Abstract

Background: Heparin-induced thrombocytopenia (HIT) is an immune-mediated adverse response to heparin therapy, characterized by decreased platelet count and increased risk of thrombosis. HIT, without the tell-tale sign of thrombocytopenia, has rarely been described.

Key Clinical Question: Can HIT be diagnosed in the presence of thrombocytosis? What clinical clues and diagnostic tools facilitate accurate diagnosis in such cases?

Clinical Approach: We report a case of HIT with thrombocytosis in a young male who initially presented after traumatic knee dislocation. HIT was diagnosed clinically through the discovery of a white thrombus during a vascular surgery procedure and corroborated by a positive latex immunoturbidimetric immunoassay (HemosIL HIT-Ab $_{(\text{platelet-factor 4(PF4)-heparin})}$), a rapid immunoassay.

Conclusion: With its high sensitivity, specificity, and rapid results, the latex immunoturbidimetric immunoassay is a valuable diagnostic tool, even among patients with a seemingly low pretest probability. This case underscores the guidance imparted by Dr Andreas Greinacher: "[HIT] must be considered if thrombosis occurs or progresses despite effective heparinization even in the absence of thrombocytopenia." Access to rapid and effective laboratory testing reduces the probability of diagnostic error.

KEYWORDS
heparin, immunoassay, platelet factor 4, thrombocytosis, thrombosis

Essentials

- Heparin-induced thrombocytopenia is a well-known highly prothrombotic condition.
- We report a case of heparin-induced thrombosis with thrombocytosis and vascular complications.
- Clinicians should apply the 4Ts if thrombosis occurs on heparin, regardless of platelet count.
- Rapid immunoassays can be helpful in cases in which pretest probability is difficult to determine.

1 | INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a well-recognized immune-mediated adverse response to heparin therapy, characterized by platelet activation, decreased platelet count, and increased risk of thrombosis. The use of unfractionated heparin and low-molecular-weight heparin remains prevalent in hospital settings, with 12 million patients in the United States exposed to heparin annually [1]. The incidence of HIT varies based on the type of heparin administered, duration of exposure, and patient population [2].

Reports of HIT without absolute or relative thrombocytopenia are rare [3–10]. The absence of thrombocytopenia poses a diagnostic challenge, necessitating a heightened level of clinical suspicion to promptly identify this potentially life-threatening complication. Established diagnostic algorithms for HIT include clinical probability assessment to guide initial management, followed by a sensitive immunoassay and confirmatory testing with a more specific functional assay. These assays are often unavailable at local hospitals necessitating send-out testing with increased turnaround time [11]. Modern rapid immunoassay (RI) use is increasing worldwide and offers strategic improvement in management. We present a case of heparin-induced thrombosis with thrombocytosis diagnosed clinically in the operating room and supported by RI testing. This case reinforces our understanding of HIT and highlights the limitations of current diagnostic tools, emphasizing the need for innovative testing methodologies to expedite accurate and timely confirmation of the disease.

2 | CASE

A 17-year-old male with no past medical history experienced a traumatic right knee dislocation during a wrestling tournament. He underwent onsite reduction by a physician at the tournament before presenting to the emergency department (ED). In the ED, pulses were reported palpable, imaging results were negative for fracture or dislocation, and he was discharged home. Two days later, he experienced leg weakness and decreased sensation, prompting return to the ED. An angiogram revealed a segmental occlusion of the popliteal artery, which was initially treated with catheter-directed thrombolysis. Overnight, he developed significant swelling and worsening acute limb ischemia. Vascular surgery performed a popliteal to posterior tibial artery bypass graft surgery and multiple compartment fasciotomies. Orthopedic surgery placed a knee-spanning external fixation. He was anticoagulated with a continuous unfractionated heparin infusion and transferred to our institution.

Upon arrival at our facility, significant necrotic muscle and persistent motor and sensory deficits below the level of the knee were observed. He subsequently required serial muscle debridements of all 4 calf compartments with ongoing heparin administration. On hospital day 9, sudden loss of distal pulses raised concern for graft thrombosis with outflow obstruction. Vascular surgery was attempted to salvage the graft by performing a graft thrombectomy, during which they identified a "white clot" [12]. Suspecting HIT, vascular surgery immediately discontinued heparin, initiated a continuous argatroban infusion, and consulted hematology. With platelet count rising throughout the hospital course (618×10^9/L on day 12 post-operatively) (Figure), the hematology consultant felt a 4Ts score could not be calculated and recommended RI testing. A positive result returned (2.3 U/mL; reference range, <1.0 U/mL) 50 minutes after the blood draw. Following an attempted thrombectomy, vascular surgery noted compromised distal outflow. The patient experienced re-occlusion of his bypass graft leading to extensive necrosis, loss of viability, and below-the-knee amputation. The serotonin release assay (SRA) returned from the Versiti Blood Research Institute 6 days later, confirming the presence of heparin-dependent platelet-activating antibodies (43% [0.1 U/mL]; 15% [100 U/mL]) and hence a likely diagnosis of HIT. Argatroban was transitioned to apixaban as the patient stabilized. The platelet count remained elevated before gradually normalizing through the remainder of the hospital course (Figure).

3 | DISCUSSION

The term "white clot syndrome" was coined in 1957 after platelet-rich white thrombi were observed in patients on heparin therapy [13]. Routine platelet counts were not common at this time, so the connection with thrombocytopenia was only established several years later [14]. Today, blood counts are regularly performed in hospitalized patients, often leading to the incidental identification of thrombocytopenia. Most patients with HIT present with a low platelet count, which usually precedes thrombosis and thus serves as an early warning [15]. The 4Ts score, a validated pretest probability tool, can assist with assessment and initial management. Unfortunately, traditional laboratory testing can be time-consuming and labor-intensive. Thus, initial management decisions must be made at bedside due to the potential for severe complications of the disease. In our case, thrombocytosis misled the hematologists, diverting suspicion away from HIT and application of the 4Ts score based on the misinterpretation that platelets must decrease in this disease. Searching the literature as the case unfolded, Dr Frank Edwin's cautionary insight added valuable context: "The name [HIT] suggests obligatory thrombocytopenia, yet HIT may still occur without thrombocytopenia, a diagnostic trap for the unwary clinician" [16].

Further review with Dr Theodore Warkentin, who developed the 4Ts score [17], clarified that the criterion of "Timing" can be assessed by the occurrence of thrombosis rather than platelet drop: "If a thrombotic event occurs within the HIT window, the patient can be judged to have at least 4 points (Timing = 2 points; Thrombosis = 2 points), so HIT is a possibility, even if there is no platelet count fall" (personal communication, included with permission, May 30, 2024). In our case, popliteal artery thrombosis first occurred before heparin initiation. Popliteal artery injuries necessitating surgical intervention are a relatively uncommon (2%) complication of knee dislocation [18]. Despite this and the lack of a family history or known hypercoagulable risk factors, the thrombus can still be rationalized considering the anatomical location of the popliteal artery, especially given the concurrent neurological deficit as the same

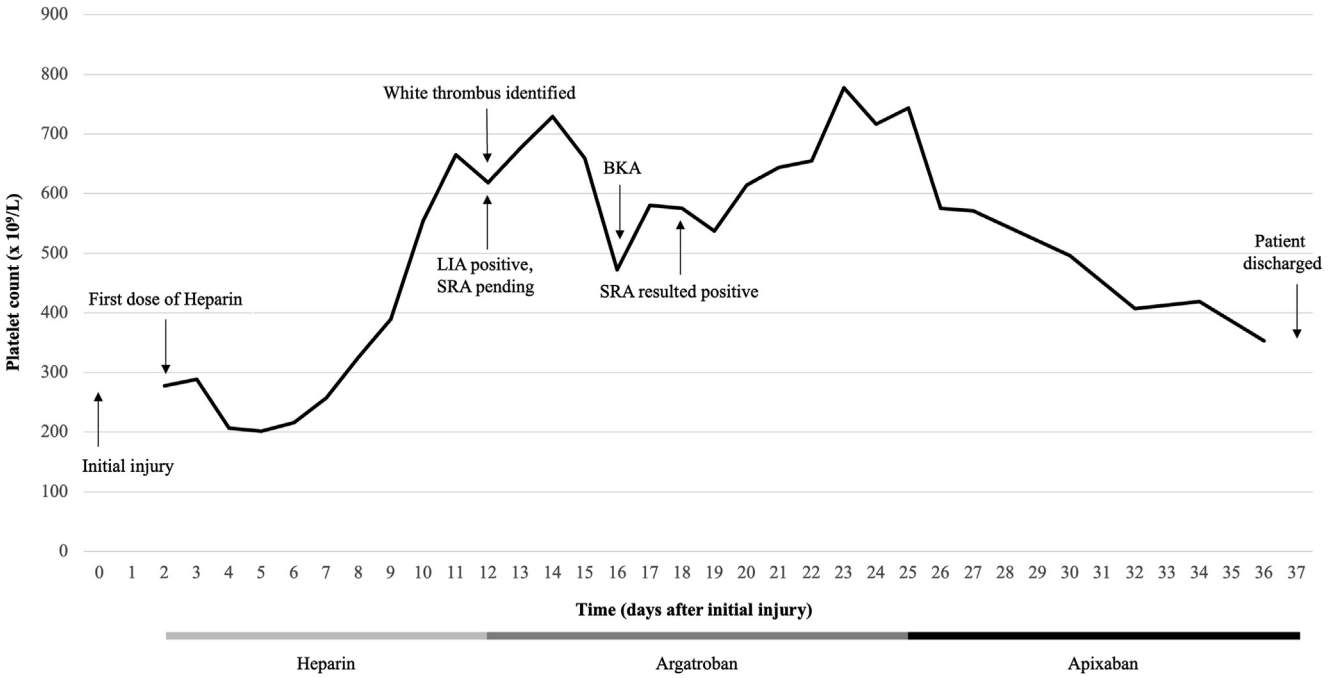

FIGURE Timeline of platelet count throughout the hospital course, highlighting significant events including medication administration, white thrombus identification, LIA, and SRA status, BKA. BKA, below-knee amputation; LIA, latex immunoturbidimetric immunoassay; SRA, serotonin release assay.

mechanism leading to nerve injury can cause vascular injury in the popliteal space. In retrospect, the initial injury may have involved a traumatic dissection without loss of pulses followed by the development of a flow-limiting prothrombotic nidus. Consequently, the recurrence of thrombosis in our patient once on heparin therapy should raise concern for HIT, irrespective of platelet count. Dr Warkentin further highlighted that the "[4Ts score should] get the clinician to consider a 'possible' diagnosis of HIT because clots are not supposed to occur when heparin is being given, although, of course, they can, both for HIT and non-HIT reasons" (personal communication, included with permission, May 30, 2024).

The question of HIT presenting with normal or elevated platelet counts is difficult to answer. One possible explanation is postoperative thrombocytosis, which coincides with the time frame of HIT, typically 5 to 10 days following heparin administration [19,20]. In our case, multiple procedures may have led to a concurrent rise in postoperative platelet count, masking the effects of HIT. This is in line with cases of HIT without thrombocytopenia that have been observed primarily in surgical and critically ill patients. The balance between reactive thrombocytosis and platelet consumption can make a HIT diagnosis challenging. Notably, reactive thrombocytosis can also occur in other common conditions such as infection, bleeding, iron deficiency, asplenia, malignancy, and inflammatory disorders. However, this is only a partial explanation, as reactive thrombocytosis is common, whereas HIT without thrombocytopenia is rare. Further, most postoperative and critically ill patients who experience HIT still exhibit thrombocytopenia despite expected reactive thrombocytosis. Additional drivers influencing the clinical presentation of HIT need to be identified.

For patients with an intermediate to high 4Ts score, laboratory testing is recommended to support a diagnosis of HIT. Two classes of assays exist: immunoassays, such as the enzyme-linked immunosorbent assay (ELISA) and RIs, and functional assays, such as the SRA, which is considered the diagnostic standard for HIT. Historically, the ELISA has been the most widely used test [21]. It is highly sensitive (97%), with a lower specificity (82%) [22]. The American Society of Hematology Choosing Wisely campaign advises against ELISA testing among patients with a low pretest probability due to high false-positive rates which may misdirect care [23]. The SRA is highly specific but poses challenges due to technical complexity, cost, and often days-long turnaround time, as testing is limited to specialized laboratories [11]. Clinicians should not wait for confirmatory SRA results, as timely initiation of treatment is imperative to reduce poor outcomes [15]. An accurate test with a rapid turnaround time and strong correlation to SRA results can be critical for patient care.

Known limitations of the 4Ts score and traditional assays enhance the utility of RIs. The latex immunoturbidimetric immunoassay (LIA) is marketed as a fully automated and on-demand qualitative assay with rapid clinical turnaround time and high sensitivity and specificity [24]. In addition to the LIA, several other RIs are in clinical use worldwide, also exhibiting high sensitivity (0.96-1.00), though with more variable specificity (0.68-0.94) [25]. In our case, the LIA produced a result within 50 minutes, promptly supporting the decision to implement alternative anticoagulation. With its high sensitivity, specificity, and rapid results, the LIA proves to be a valuable diagnostic tool, even among patients with a seemingly low pretest probability. Given these advantages, RIs have become the most frequently ordered laboratory

test for HIT, recently surpassing the ELISA, which accounted for 47% of immunoassays ordered from 2013 to 2017. Despite this, many labs continue to rely on the ELISA [26]. Increased guidance on incorporating RIs into diagnostic algorithms is needed [25].

The interplay between clinical judgment and laboratory testing is complex in this highly prothrombotic disease. Reports of HIT without reduced platelet counts in both pediatric [4,7,9] and vascular surgery [3,6,8] cases underscore the guidance imparted by Dr Andreas Greinacher: "[HIT] must be considered if thrombosis occurs or progresses despite effective heparinization even in the absence of thrombocytopenia" [4]. Clinicians must remain vigilant when presented with a patient who develops thrombosis on heparin and should initiate early management and testing of HIT. Access to rapid and effective laboratory testing reduces the probability of diagnostic error.

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J.L. and M.S. drafted the manuscript with critical input and revisions from H.D.S., L.L., M.V., and R.P.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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