Severe Autoimmune LMWH-Induced Thrombocytopenia Presenting with Aortic Thromboses, Adrenal Hemorrhage and Pulmonary Embolism: Response to High-Dose Intravenous Immunoglobulin

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Abstract
The occurrence of heparin-induced thrombocytopenia (HIT) in the setting of low-molecular-weight heparin (LMWH) exposure is uncommon, with incidence reported at around 0.2%. Delayed-onset (autoimmune) HIT in the setting of LMWH use is rarer, with only two other case reports in the literature.

An 83-year old man was admitted to hospital for an acute exacerbation of chronic obstructive pulmonary disease, receiving LMWH, (tinzaparin) while in hospital for prophylaxis against deep venous thrombosis (DVT). One day after discharge, he presented to the emergency department with acute chest pain and dyspnea. Computed tomography revealed bilateral pulmonary embolism, multiple abdominal aortic thromboses, and unilateral adrenal hemorrhage, and he was given a bolus of intravenous unfractionated heparin (UFH) in the emergency department. His platelet count (prior to UFH bolus) was found to be markedly reduced ($39 \times 10^9/L$) from normal values two days prior. We suspected heparin-induced thrombocytopenia (HIT) to have caused the thrombocytopenia and thromboses (arterial and venous), and thus anticoagulation therapy was changed from heparin to argatroban. His HIT assay was strongly positive, including features of autoimmune reactivity (serum-induced platelet activation in the absence of heparin). HIT developing after exposure to tinzaparin is relatively rare and use of a scoring system helped to facilitate an early diagnosis. Additionally, this case demonstrates heparin-independent platelet activation, a marker for autoimmune HIT (aHIT).

The patient’s serum tested strongly positive for IgG-specific anti-PF4/heparin EIA and serotonin-release assay. The presence of these antibodies would also explain the further decline in
his platelet count to $10 \times 10^9$/L after he received a bolus dose of heparin at the beginning of his second hospitalization. This case highlights the third reported case of delayed-onset HIT in the setting of LMWH, and the rapid response to high-dose intravenous immunoglobulin.

**Background**

Although rare, delayed-onset HIT has been described following administration of low-molecular weight heparin, and the condition must be suspected in patients presenting thrombosis and thrombocytopenia given recent exposure to LMWH. We present a case of severe autoimmune LMWH-induced thrombocytopenia.

**Figure 1** Contrast-enhanced CT scans showing multiple aortic thrombi in the distal abdominal aorta (A, B), right adrenal hemorrhage (B), and a pulmonary embolism (C).
describe our experience with a patient in whom HIT caused aortic thromboses, bilateral pulmonary emboli (PE), and unilateral adrenal hemorrhagic necrosis after exposure to tinzaparin for DVT prophylaxis.

**Case Presentation**

An 83-year old man with a history of chronic obstructive pulmonary disease (COPD) and osteoarthritis presented to the emergency department complaining of acute right flank pain and sharp chest pain radiating to his back. A contrast-enhanced computed tomography (CT) scan of the aorta was ordered by the emergency physician to rule out aortic dissection. The CT scan revealed bilateral PE in addition to multiple arterial thrombi in the abdominal aorta and a right adrenal hemorrhage (Figure 1). Of note, he was thrombocytopenic at his second presentation, with a platelet count of 39 × 10^9/L.

He received a single bolus of 6000 units of intravenous heparin in the emergency department prior to consultation with the admitting medicine team. His 4Ts score (refer to Table 1 below) at the time was 6, based upon: (a) >50% platelet count fall from 200 to 39 (2 points); (b) onset of thrombocytopenia within 4 days of heparin use (0 points); (c) proven thromboses (2 points); and (d) absence of another plausible explanation (2 points). As HIT was suspected to be the underlying etiology for the thrombocytopenia and thromboses, the patient had his anticoagulation changed from heparin to argatroban and hematology was consulted for further investigations and management. Review of his medication history concluded that apart from the four days of LMWH exposure, the patient had no exposure to heparin in the last hundred days, excluding potential immunization secondary to heparin flushes (as the patient was hospitalized for approximately 18 hours prior to his first documented dose of tinzaparin). Although HIT was the favoured diagnosis, other initial diagnostic considerations included antiphospholipid antibody syndrome or immune thrombocytopenic purpura (ITP).

Initial investigations revealed a platelet count of 39 × 10^9/L, a hemoglobin of 126 g/L, a white blood cell count of 9.8 × 10^9/L, an international normalized ratio of 1.1, and an activated partial thromboplastin time of 32 seconds. Both the INR and PTT were somewhat elevated compared with the values observed during the previous admission (1.0 and 28 seconds, respectively). Hemolytic workup was negative (lactate dehydrogenase [LDH] was 225 U/L [120–230 U/L]), and peripheral blood smear showed isolated thrombocytopenia. His fibrinogen level was low-normal (1.79 g/L [1.50-4.50 g/L]). JAK2 V617F mutation was negative. Results for lupus anticoagulant were invalid as patient was receiving anticoagulation with argatroban at the time of testing. However, anti-cardiolipin IgG and IgM antibodies were negative, and anti-beta 2 glycoprotein I IgG antibody was also negative.

The patient continued therapeutic argatroban while the results of his workup were pending. Over the subsequent four days in hospital, his platelet count continued to decline to reach

| Table 1. The Warkentin 4T Score Probability Scale for HIT |
|----------------------------------------------------------|
| **Thrombocytopenia**                                      |
| – 2 points if >50% decrease in platelet count to a platelet nadir of ≥20 x 10^9/L |
| – 1 point if 30-50% decrease in platelet count, or if the nadir is 10-19 x 10^9/L |
| – 0 points if <30% decrease in platelet count, or if the nadir is <10 x 10^9/L |
| **Timing of onset of decrease in platelet count**        |
| – 2 points if onset is 5–10 days after starting heparin, or <1 day if there has been recent heparin use (within past 30 days) |
| – 1 point if onset is >10 days after starting heparin or if timing is unclear; or if <1 day after starting heparin with recent heparin use (past 31–100 days) |
| – 0 points if onset within four days of first time heparin use |
| **Thrombosis or other sequelae**                          |
| – 2 points if there is a proved new thrombosis, skin necrosis, or acute systemic reaction after intravenous unfractionated heparin use |
| – 1 point if there is progressive or recurrent thrombosis, erythematous skin lesions at injection sites, or suspected thrombosis (not proved) |
| – 0 points if there is no thrombosis or other findings |
| **Other causes of decrease in platelet count**            |
| – 2 points if none evident |
| – 1 point if there is another possible cause |
| – 0 points if there is another definite cause |
| **Pretest probability scores:**                           |
| – High: 6–8 points |
| – Intermediate: 4–5 points |
| – Low: 0–3 points |

units of subcutaneous tinzaparin daily for DVT prophylaxis. His platelet count at discharge on day 3 was 200 × 10^9/L (first day of tinzaparin administration = day 0). He presented back to the emergency department one day after discharge (i.e., day 4 post-start of tinzaparin) complaining of acute right flank pain and sharp chest pain radiating to his back. A contrast-enhanced computed tomography (CT) scan of the aorta was ordered by the emergency physician to rule out aortic dissection. The CT scan revealed bilateral PE in addition to multiple arterial thrombi in the abdominal aorta and a right adrenal hemorrhage (Figure 1).
a nadir of \(10 \times 10^9/L\). Although he had no clinical bleeding, the continued decline prompted his heparin therapy to be suspended for two days. The rationale was to treat potential ITP as results of the HIT antibody testing were still pending, and a platelet nadir of 10 with continued decline was felt to be inconsistent with HIT. The day following his first dose of IVIg, his HIT assay returned positive, and because high-dose IVIg has been reported to raise platelet counts in patients with severe or persisting HIT, it was decided to continue with the second dose of IVIg. His platelets abruptly responded, rising to \(27 \times 10^9/L\) after the first dose and \(47 \times 10^9/L\) after the second dose.

The HIT assay was sent to the McMaster Platelet Immunology Laboratory in Hamilton, Ontario, Canada. Both the platelet factor 4-dependent immunoassay as well as the confirmatory serotonin-release assay (SRA) were strongly positive, thus confirming the diagnosis of HIT in this patient. The IgG-specific anti-PF4/heparin enzyme-immunoassay (EIA) was strongly positive (2.169 optical density [OD] units; normal, <0.450) and the platelet SRA was also strongly positive (100% serotonin-release at 0.1 and 0.3 IU/mL UFH [normal, <20%]), with inhibition to 4% at 100 IU/mL heparin); in addition, heparin-independent serum-induced platelet activation was shown, as 100% serotonin-release was also seen at 0 IU/mL UFH (“buffer control”). Such strong serum-induced platelet activation in the absence of heparin in a patient who otherwise tests strongly positive for HIT antibodies is a feature of autoimmune HIT (aHIT) disorders, such as “delayed-onset HIT” , “persisting HIT” , and “spontaneous HIT” syndromes (see Table 2). Our patient met the definition of delayed-onset HIT, which is a case meeting both clinical and serological criteria for HIT and where the platelet count either begins to fall or worsens after stopping all heparin. 

The patient continued therapeutic anticoagulation with argatroban while awaiting further increase in his platelet count before transitioning to rivaroxaban. We chose to transition from argatroban to rivaroxaban, for several reasons: first, if the HIT recurred after the effect of high-dose IVIg wore off, the patient would be at risk of warfarin-associated microthrombosis (e.g., warfarin-associated venous limb gangrene), which is the reason why warfarin is contraindicated during acute HIT; second, there is consistently favourable experience using rivaroxaban in case-series of patients with serologically confirmed HIT including a prospective cohort study. Evidence that rivaroxaban was effective in our patient included: (a) lack of thrombotic events while on this direct oral anticoagulant; (b) gradual decrease in D-dimer levels (which we measured every month post-discharge); and (c) gradual increase in plasma fibrinogen levels (which we measured every day), supporting control of HIT-associated consumptive coagulopathy. The course of the platelet count is outlined in Figure 2.

Table 2 Autoimmune Heparin-Induced Thrombocytopenia Syndromes

| Clinical Entity | Description |
|-----------------|-------------|
| Delayed-onset HIT | HIT that begins or worsens after stopping of heparin |
| Persisting HIT | HIT that persists for > 1 week despite stopping of heparin |
| Spontaneous HIT syndrome | HIT without proximate heparin exposure |

Adapted from Greinacher et al., 2017

Discussion and Conclusions

Heparin-induced thrombocytopenia is an immune-mediated disorder activated by exposure to commonly used anticoagulants: UFH, LMWH, and fondaparinux. These medications trigger the production of platelet-activating IgG antibodies which bind to platelet factor 4 (PDF4)-heparin complexes, causing platelet consumption and thrombosis. Thromboses may present classically as DVT or PE, or more unusual complications such as unilateral or bilateral adrenal hemorrhage (secondary to adrenal vein thrombosis), transient global ischemia, and cerebral vein thrombosis.

Delayed-onset HIT is diagnosed when this thrombocytopenia begins or worsens even in the absence of heparin. It is characterized by an incident exposure to UFH, discontinuation of UFH, and subsequent development of thrombocytopathy and thrombosis after stopping of heparin. The name “delayed-onset” initially described HIT starting after heparin had been stopped, but is now recognized to be a misnomer as most cases have the usual onset of day 5–10 after immunizing exposure. Our patient presented with several clinical features consistent with delayed-onset HIT: he had a previous exposure to LMWH (tinzaparin), a platelet decline of >50%, and proven thromboses (PE, aortic thromboses, and unilateral adrenal hemorrhage) in the absence of another plausible explanation. The diagnosis was serologically confirmed, with a strongly positive IgG-specific anti-PF4/heparin EIA and SRA (including strong serum-induced platelet activation in the absence of heparin, a serological marker of delayed-onset HIT).

The occurrence of HIT in the setting of LMWH exposure is uncommon, ten-fold less than UFH (2.6%) with an incidence reported at 0.2%. Delayed-onset HIT in the setting of LMWH use is rarer, with only two other case reports in the literature in 2008 and 2012. LMWH-induced HIT tends to be more severe, with severe thrombocytopenia (platelets < 15 x 10^9) occurring more often than in UFH-induced HIT. In heparin naïve patients, studies have shown that it takes four days for anti-PF4/heparin
antibodies to develop\textsuperscript{21,22}; we did confirm that our patient did not receive prior UFH, LMWH, or fondaparinux within the previous 100 days. It is rare to see such a fall in platelets earlier than five days, and is one of the unique aspects of this case. Nevertheless, the patient had been hospitalized for approximately 18 hours prior to his first dose of prophylactic tinzaparin, and we cannot exclude the possibility that he received a heparin flush through his peripheral IV prior to that, which would make this case day five onset.

The use of IVIg is emerging as a new therapy for HIT, particularly autoimmune HIT (aHIT). Dosing is typically 1 g/kg given daily over two days, in the identical dosing regimen as ITP. IVIg to treat HIT was first described in 1994.\textsuperscript{23} Recent data shows that high-dose IVIg interrupts HIT antibody-induced platelet activation, in a dose-dependent fashion, via Fc receptors on platelet surfaces.\textsuperscript{5} Although consensus guidelines recommend against using IVIg to treat HIT, as newer reports surface, some authors now advocate for high-dose IVIg to be second-line therapy for the management of aHIT.\textsuperscript{5,23} IVIg appears to be particularly effective for aHIT, as recent reports show a high likelihood of abrupt platelet recovery after administration of high-dose IVIg.\textsuperscript{24} Similar to our case, features included very low platelet count nadirs (median, 15 x 10\textsuperscript{9}/L) and persistence of thrombocytopenia until administration of IVIg.\textsuperscript{24} Importantly, aggressive anticoagulation is still necessary after use of IVIg.\textsuperscript{5}

We described our experience with a patient in whom unusually severe autoimmune HIT secondary to tinzaparin exposure caused multiple aortic thromboses, unilateral adrenal hemorrhage, and bilateral pulmonary emboli, with a platelet nadir of 10 x 10\textsuperscript{9}/L that responded abruptly to administration of IVIg. If thrombocytopenia develops with thrombosis in the context of recent LMWH or unfractionated heparin exposure, HIT should be strongly suspected to avoid fatal complications.

Declarations

- Ethics approval and consent to participate: Not applicable.
- Consent for publication: Written consent for publication of this case report was obtained from the patient.
- Availability of data and materials: All data generated or analyzed during this study are included in this published article [and its supplementary information files].
- Competing interests: TEW has received lecture honoraria from GlaxoSmithKline, Pfizer Canada, and Sanofi-Aventis, has provided consulting services to, and/or has received research funding from, Canyon Pharmaceuticals, GTI Diagnostics Inc, GlaxoSmithKline, and Paringenix, and has provided expert witness testimony relating to heparin-induced thrombocytopenia.
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• Authors’ contributions: JN drafted the manuscript. PA assisted with data collection and contributed to the discussion. TEW provided the laboratory results from the McMaster Platelet Immunology Laboratory and was a major contributor to the manuscript. OM assisted with medical follow up of the patient and ongoing monitoring. All authors approved of the final version of the manuscript.

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References
1. Alsaleh KA, Al-Nasser SMA, Bates SM, Patel A, Warkentin TE, and Donald MA. Delayed-onset HIT caused by low-molecular-weight heparin manifesting during fondaparinux prophylaxis. Am J Hematol 2008;83:876–78.
2. Kumar M, Abrina VM, Chittimireddy S. Pulmonary embolism caused by delayed heparin-induced thrombocytopenia in a patient who received prophylactic LMWH. Am J Case Rep 2012;13:118–21.
3. Cuker A, Gimotty PA, Crowther MA, Warkentin TE. Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: a systematic review and meta-analysis. Blood 2012;120:4160–7.
4. Warkentin TE, Anderson JAM. How I treat patients with a history of heparin-induced thrombocytopenia. Blood 2016 Jul 21;128(3):348–59.
5. Greinacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. J Thromb Haemost 2017 Nov;15 (11):2099–114. doi: 10.1111/jth.13813. Epub 28 Sep 2017. [PMID: 28846826].
6. Warkentin TE, Kelton JG. Delayed-onset heparin-induced thrombocytopenia and thrombosis. An Intern Med 2001;135(7):502–506.
7. Kopolovic I, Warkentin TE. Progressive thrombocytopenia after cardiac surgery in a 67-year-old man. CMAJ 2014 Sep 2;186(12):929–33.
8. Warkentin TE, Basciano PA, Knopman J, Bernstein RA. Spontaneous heparin-induced thrombocytopenia syndrome: 2 new cases and a proposal for defining this disorder. Blood 2016;123(23):3651–54.
9. Warkentin TE, Greinacher A. Management of heparin-induced thrombocytopenia. Curr Opin Hematol 2016 Sep;23(5):462–70.
10. Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia. American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133(6 Suppl):S305–380S.
11. Linkins LA, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, Crowther M; American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e495S–530S.
12. Ng HJ, Than H, Teo EC. First experiences with the use of rivaroxaban in the treatment of heparin-induced thrombocytopenia. Thromb Res 2015 Jan;135(1):205–7.
13. Ong SY, Chin YA, Than H, Tan CW, Yap ES, Wong WH, Ng HJ. Rivaroxaban for heparin-induced thrombocytopenia: adding to the evidence. Ann Hematol 2016 Nov 7. [Epub ahead of print]
14. Linkins LA, Warkentin TE, Pai M, Shivakumar S, Manji RA, Wells PS, Wu C, Nazi I, Crowther MA. Rivaroxaban for treatment of suspected or confirmed heparin-induced thrombocytopenia study. J Thromb Haemost 2016 Jun;14(6):2106–210.
15. Kurtz L, Yang S. Bilateral adrenal hemorrhage associated with heparin induced thrombocytopenia. Am J Hematol 2007;82:493–94.
16. Warkentin TE, Safyan EL, Linkins LA. Heparin-induced thrombocytopenia presenting as bilateral adrenal hemorrhages. N Engl J Med 2015 Jan;372(5):492–4.
17. Warkentin TE, Bernstein RA. Delayed-onset heparin-induced thrombocytopenia and cerebral thrombosis after a single administration of unfractionated heparin. N Engl J Med 2003;348:1067–69.
18. Pohl C, Harbrecht U, Greinacher A, Theuerkauf I, Biniek R, Hanfland P, Klockgether T. Neurologic complications in immune-mediated heparin-induced thrombocytopenia. Neurology 2000;54:1240–50.
19. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005;106:2710–715.
20. Gruel Y, Poupard C, Nguyen P, Borg J, Derlon A, Juhan-Vague I, Regnault V, Samama M. Biological and clinical features of low-molecular-weight heparin-induced thrombocytopenia. Br J Haematol 2003;121:786–92.
21. Warkentin TE. Clinical picture of heparin-induced thrombocytopenia (HIT) and its differentiation from non-HIT thrombocytopenia. Thromb Haemost 2016;116:813–22.
22. Greinacher A, Kohlmann T, Strobel U, Sheppard JA, Warkentin TE. The temporal profile of the anti-PF4/heparin immune response. Blood 2009;113:4970–76.
23. Greinacher A., Liebenhoff, U., Kiefel, V., Presek, P., and Mueller-Eckhardt, C. Heparin-associated thrombocytopenia: the effects of various intravenous IgG preparations on antibody mediated platelet activation—a possible new indication for high dose i.v. IgG. Thromb Haemost 1994;71:641–64.
24. Tivto A, Bakchoul T, Rowe JM, Greinacher A, Ganzel C. Severe and persistent heparin-induced thrombocytopenia despite fondaparinux treatment. Am J Hematol 2015;90:675–8.