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.

RESUME
La survenue d'une thrombo-cytopénie induite par l'héparine (TIH) dans le cadre d'une exposition à l'héparine de faible poids moléculaire (HFPM) est rare, l'incidence étant de l'ordre de 0,2%. L'apparition retardée (auto-immune) dans le cadre de l'utilisation de l'HFPM est plus rare, avec seulement deux autres rapports de cas dans la littérature.

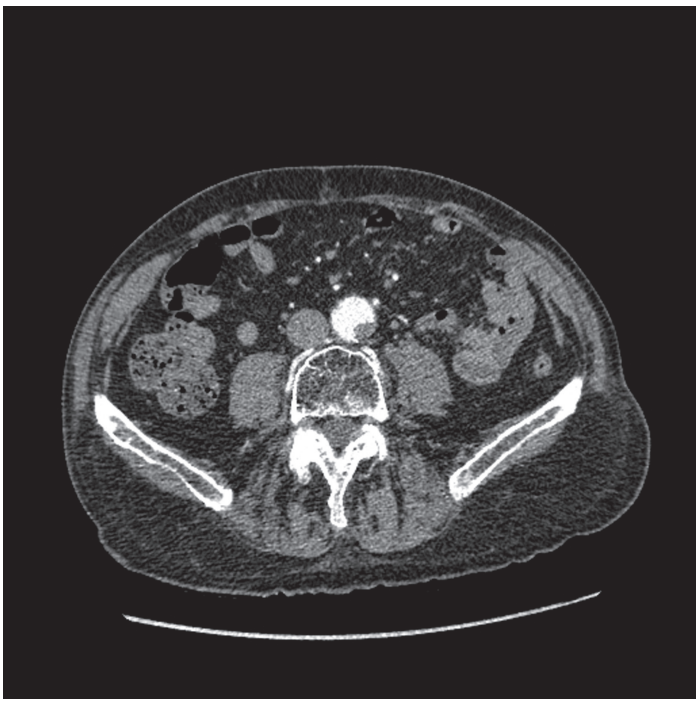
An 83-year old man was admitted to hospital for an acute exacerbation of chronic obstructive pulmonary disease, receiving LMWH, (tinzaparin) while in hospital for prophylaxis against deep venous thrombosis (DVT). One day after discharge, he presented to the emergency department with acute chest pain 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 (39×10^9/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 10×10^9/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,[1,2] and the condition must be suspected in patients presenting thrombosis and thrombocytopenia given recent exposure to LMWH. We



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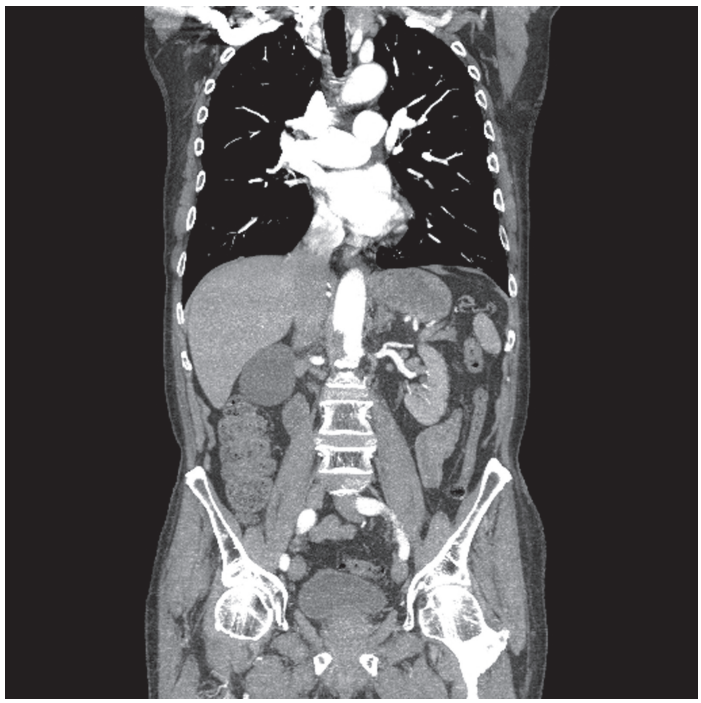

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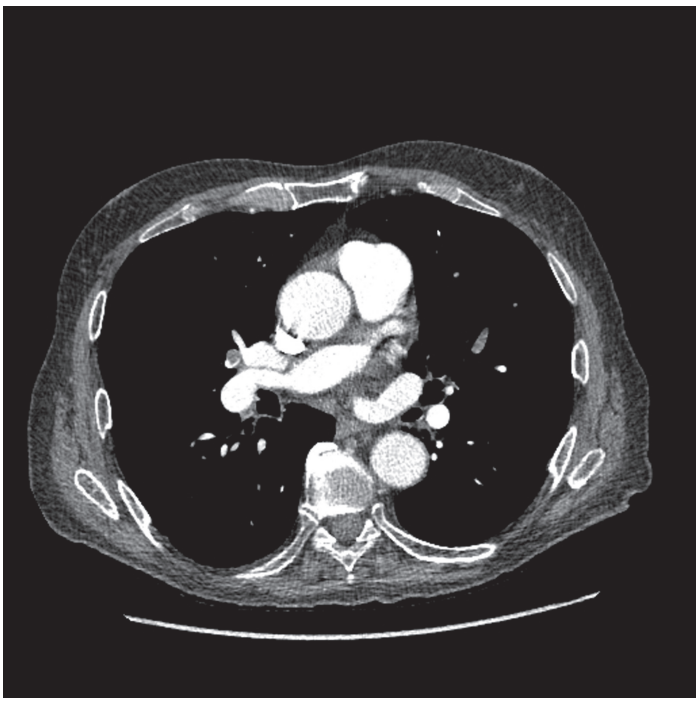

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Figure 1 Contrast-enhanced CT scans showing multiple aortic thrombi in the distal abdominal aorta (A, B), right adrenal hemorrhage (B), and a pulmonary embolism (C).

Table 1. The Warkentin 4T Score[3] 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

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 a one-week history of increased cough, sputum production, and dyspnea. He was afebrile, mildly tachycardic, and hypoxic requiring 4 liters of supplemental oxygen. He had a normal complete blood count (platelets of 160 x 10^9/L) with a chest radiograph showing hyperinflation with no consolidation or evidence of heart failure. He was admitted to the medicine unit for treatment of an acute COPD exacerbation with inhalers, but no antibiotics or steroids. During this initial hospitalization, he received 4500 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). 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[3] (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

a nadir of 10×10^9/L. Although he had no clinical bleeding, the continued decline in his platelet count despite therapeutic anticoagulation prompted initiation of high-dose intravenous immunoglobulin G (IVIg) therapy at 1 g/kg 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[4,5] it was decided to continue with the second dose of IVIg. His platelets abruptly responded, rising to 27×10^9/L after the first dose and 47×10^9/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.[5–9] 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.[9,10,23]

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[10,11]; second, there is consistently favourable experience using rivaroxaban in case-series of patients with serologically confirmed HIT[12,13] including a prospective cohort study.[14] 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[23]

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.[16] 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.[15–18]

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 thrombocytopenia and thrombosis after stopping of heparin.[6] 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.[5] 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[5]).

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%.[19] Delayed-onset HIT in the setting of LMWH use is rarer, with only two other case reports in the literature in 2008[1] and 2012.[2] LMWH-induced HIT tends to be more severe, with severe thrombocytopenia (platelets < 15 x 10^9) occurring more often than in UFH-induced HIT.[20] In heparin naïve patients, studies have shown that it takes four days for anti-PF4/heparin

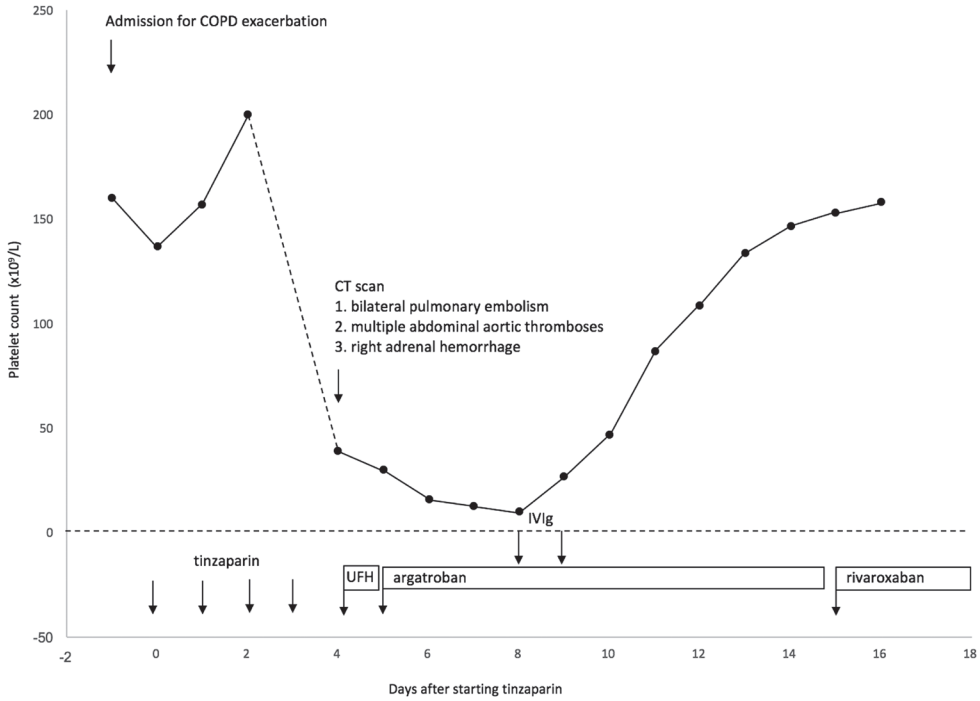

Figure 2. Time course of the platelet count and exposure to anticoagulants. The platelet count decreased 4 days after first exposure to tinzaparin.

antibodies to develop[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.[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.[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.[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.[24] Similar to our case, features included very low platelet count nadirs (median, 15 x 10^9/L) and persistence of thrombocytopenia until administration of IVIg.[24] Importantly, aggressive anticoagulation is still necessary after use of IVIg.[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 10×10^9/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.
- Funding: No funding was provided for this case report.

- 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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