CASE REPORT

Early recognition is the key to success: pulseless electrical activity (PEA) as a manifestation of heparin-induced anaphylactoid reaction

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SUMMARY

A 64-year-old man underwent mitral valve replacement. He was hospitalised 9 days later because of slurring of speech and left-sided facial weakness. During hospitalisation, unfractionated heparin (UFH) bolus and drip were initiated due to subtherapeutic international normalised ratio. Within 5 min of UFH bolus, the patient began to experience symptoms of dyspnoea, followed by pulseless electrical activity arrest. He was successfully resuscitated. A decline in platelet count >50% was noted immediately after UFH bolus and cardiac arrest. A diagnosis of heparin-induced thrombocytopenia and anaphylactoid reaction was considered (4Ts score of 7). Heparin was discontinued and argatroban was started. A platelet factor 4 (PF4) assay was strongly positive. Platelet counts subsequently improved following discontinuation of heparin.

BACKGROUND

Heparin-induced thrombocytopenia (HIT) is an adverse immune-mediated reaction that occurs following exposure to unfractionated heparin (UFH) and, less commonly, to low-molecular-weight heparin (LMWH)¹ (OR 0.13 (0.03 to 0.33), $p=0.0002$).² Among the several risk factors for the development of HIT, cardiac surgery poses a 15–20% risk of antibody occurrence.³ HIT can manifest in various ways, from isolated thrombocytopenia and thrombosis to unusual features such as skin necrosis, adrenal haemorrhagic infarction and anaphylactoid reactions, following a bolus of intravenous UFH.⁴ Acute systemic reactions can occur in up to 25% of patients with pre-existing HIT antibodies.⁵ These phenomena occur in conjunction with a decline in platelet count; that is, they occur in association with HIT rather than as an isolated reaction to heparin.⁶

We present a case of a 64-year-old man with previous UFH exposure who suffered from acute cardiopulmonary arrest immediately following re-exposure to heparin, felt to be related to heparin-induced anaphylactoid reaction, after all other causes were excluded. A detailed discussion regarding the clinical features and pathogenesis with an emphasis on early recognition of HIT-induced anaphylactoid reactions follows. This case serves as an important clinical reminder for physicians in acute medical care settings including intensive care units.

CASE PRESENTATION

A 64-year-old man presented to the hospital because of transient left facial weakness and slurring of

speech. One day prior to presentation, he reportedly had shaking chills, shortness of breath and confusion, characteristic of short-term memory loss, lasting for 10 min. The medical history was notable for JAK 2 positive polycythaemia vera and C282Y-H63D compound heterozygous haemochromatosis on a periodic phlebotomy programme to target ferritin levels of <50 ng/mL. Nine days prior to the presentation, the patient had undergone mitral valve replacement with a 32 mm Hancock II porcine valve, for severe mitral regurgitation. During the cardiac procedure, the patient had exposure to heparin, and postoperatively he was continued on heparin and bridged with warfarin. Platelet counts on the day prior to cardiac surgery, day of surgery and postoperative day (POD) 4 were $296 \times 10^9/L$, $237 \times 10^9/L$ and $250 \times 10^9/L$, respectively. He was discharged on warfarin on POD4. The patient was not a smoker, and he neither drank alcohol nor used recreational drugs.

On neurological examination, the patient was alert, although was not oriented to time. His language skills were intact, however, his responses were slow. His short-term memory was impaired, with 0 of 4 object recollection at 5 min. Cranial nerves II–XII were intact. Motor strength was 5/5 with 2+ deep tendon reflexes throughout. No gait abnormalities were noted. Respiratory examination was abnormal with presence of crackles at the right lower base; otherwise, the remainder of the physical examination was unremarkable.

INVESTIGATIONS

Initial blood work including complete blood count (CBC), complete metabolic panel (CMP), prothrombin time/international normalised ratio (PT/INR) and infectious work up, was normal (table 1). Chest radiograph showed a right basilar opacity concerning for pneumonia. CT of the head revealed no acute changes, while a two-dimensional (2D) echocardiogram showed concentric left ventricular hypertrophy with an ejection fraction of 45%, but no new changes. Hence, the patient was placed on oral levofloxacin for presumed community-acquired pneumonia with some improvement in his cognition.

In order to determine the aetiology for the neurological deficits, the patient underwent further imaging including MRI of the head, MR angiogram (MRA) of the head and neck, and carotid duplex ultrasonography, which did not reveal any acute abnormalities.

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Table 1 Summary of the laboratory work up of patient on re-admission on day 9 (postoperative day 8)

Test	Value (units)	Normal (units)
White cell count	10.1×10 ⁹ /L	4.1–10.9×10 ⁹ /L
Haemoglobin	9.1 g/dL	12.9–17.3 g/dL
Haematocrit	27.6%	38–51%
Platelet	252×10 ⁹ /L	150–450×10 ⁹ /L
Sodium	137 mmol/L	133–144 mmol/L
Blood urea nitrogen	16 mg/dL	6–24 mg/dL
Creatinine	1.0 mg/dL	0.6–1.2 mg/dL
Aspartate transferase	20 U/L	15–46 U/L
Alanine transferase	20 U/L	10–61 U/L
Total bilirubin	0.7 mg/dL	0.4–1.4 mg/dL
Ammonia	38 µmol/L	25–55 µmol/L
International normalised ratio	2.6	0.9–1.1
Troponin I	0.1 ng/mL	0.0–0.1 ng/mL
C reactive protein	2.0 mg/dL	0.0–0.1 mg/dL
Blood cultures	No growth	No growth

Diagnosis was presumed to be a transient ischaemic attack with some acute cognitive decline secondary to recent surgery and infection. The patient had to undergo inpatient physical therapy due to moderate deconditioning leading to a slightly longer than expected hospital stay.

On day 3 of re-hospitalisation (POD11), the patient's laboratory tests were notable for normal CBC (haemoglobin of 8.6 g/dL,

white cell count of $9.1 \times 10^9/L$ and platelet count of $245 \times 10^9/L$, but a subtherapeutic INR (1.4). Hence, an order was placed to start UFH (bolus of 6000 units followed by drip) for bridging purposes. Within 5 min of starting the intravenous UFH bolus, the patient became dyspnoeic, hypotensive (systolic blood pressure dropped to 93 mm Hg) and bradycardic, with a heart rate of 50 bpm. Pulseless electrical activity eventually followed. He was successfully resuscitated with return of spontaneous circulation in 22 min. He was transferred to the medical intensive care unit for further care, where his blood pressure was maintained on pressors (dopamine and epinephrine drips) and breathing was supported on mechanical ventilation. Blood drawn at the time of cardiac arrest was notable for a drop in platelet count (245–119).

A repeat CT of the head was negative for intracranial haemorrhage, while a 2D echocardiogram did not show any evidence of focal wall motion abnormalities or evidence of cardiac tamponade. Bilateral lower extremity venous Dopplers were negative for deep venous thrombosis and the V/Q scan performed (in lieu of CT scan, as the patient had acute kidney injury) showed intermediate probability secondary to pneumonia and pleural effusion. The patient's anticoagulation was continued until his platelet count reached a nadir of $56 \times 10^9/L$ on day 6 (POD13) of hospital stay (as shown in figure 1).

TREATMENT

On the basis of the sequence of events, platelet count decline (>50% drop immediately after intravenous UFH bolus and cardiac arrest), HIT and anaphylactoid reaction were considered (4Ts score of 7). All heparin and heparinised products were

Figure 1 The patient underwent mitral valve replacement on day 0. On day 9 (postoperative day (POD) 8), on readmission, platelet levels were normal at $252 \times 10^9/L$. The patient received an unfractionated heparin (UFH) bolus and drip on POD11 for subtherapeutic international normalised ratio. Initial platelet count on day 12 prior to the UFH bolus was normal at $245 \times 10^9/L$ and subsequently dropped to $119 \times 10^9/L$ within a few hours following the anaphylactoid reaction. Platelet count trended down to a nadir of $56 \times 10^9/L$. Argatroban was started after discontinuation of heparin on day 14. Platelet count normalised over the remainder of the hospitalisation (MRV, MR venography).

discontinued. The patient was started on argatroban. ELISA for platelet factor 4 (PF4) antibody was strongly positive (2.760 once daily). The patient's platelet count improved the following day after discontinuation of heparin to a value of $188 \times 10^9/L$. He was treated with argatroban until the platelet counts were $>100 \times 10^9/L$, following which warfarin was started.

OUTCOME AND FOLLOW-UP

The patient was eventually weaned off pressors and was successfully extubated. He received inpatient rehabilitation for 16 days and was subsequently discharged in stable condition.

DISCUSSION

Heparin-induced anaphylactoid reactions are entities that were described over 50 years ago and have been quoted to affect nearly 5% of patients identified with HIT.⁶ A distinction must be made between the terms anaphylaxis and anaphylactoid in the context of heparin-induced reactions, with the former mediated through IgE-related mast cell degranulation and the latter through IgG or IgM.⁶ Anaphylactoid reactions have a wider range of clinical symptoms. The scope of this paper focuses on HIT-associated anaphylactoid reactions.

The exact mechanism of heparin-induced anaphylactoid reactions, including cardiopulmonary arrest, is not well-defined—rather—it is built on the pathophysiology of HIT. This is further supported by the subsequent decline in platelet count that accompanies heparin-induced anaphylactoid reactions. The hypotheses for HIT-associated anaphylactoid reactions explore the various theories of histamine-mediated, complement-mediated, microvascular events and mechanical obstruction. Hewitt *et al*⁷ used ELISA to describe a lack of IgE in a patient presenting with cardiopulmonary arrest immediately following intravenous UFH bolus. As with our case, previous case reports did not reveal eosinophilia. However, following a UFH bolus, widespread platelet activation in turn caused PF4 release from platelet granules. PF4 is found to cause histamine release from mast cells, as well as proteases that cleave to produce complement-mediated anaphylatoxins such as C3a, C4a and C5a.^{8,9} Yet another premise for HIT-induced anaphylactoid reactions suggests leucocyte activation and inflammation.⁶ PF4 functions as a chemoattractant for neutrophils, monocytes and eosinophils.⁹ The IgG–heparin–PF4 complexes resulting in wide-scale platelet activation may cause transient microvascular platelet aggregation and blockage.⁹ When these events occur in pulmonary or coronary vasculature, this will clinically manifest as a cardiopulmonary collapse.

Heparin-induced anaphylactoid reactions can manifest in a range of acute systemic reactions, such as fever, chills, hypertension, tachycardia, chest pain and dyspnoea, as well as life-threatening features including cardiac arrest and death (box 1).⁶

These signs and symptoms typically occur 5–30 min after administration of UFH.⁶ Intravenous bolus of UFH is more frequently associated with heparin-induced anaphylactoid reactions than UFH infusion or subcutaneous LMWH.⁶ HIT-associated anaphylactoid reactions are related to previous exposure; typically 7–100 days.⁶ In addition, all reports of HIT-associated anaphylactoid reactions are followed by an almost immediate decline in the platelet count, thus mandating the immediate measurement of platelets. Of note, in the presence of symptoms of chills and transient global amnesia, similar to what our patient reported on PODs 7 and 8, one can consider delayed-onset HIT, although a lack of relative platelet drop on POD8 ($252 \times 10^9/L$) makes the diagnosis difficult to establish. Studies have suggested that persistent antibodies, as opposed to

Box 1 Clinical features of anaphylactoid reactions following intravenous bolus heparin

- ▶ Timing: onset 5–30 min after intravenous heparin bolus (less commonly, following intravenous or subcutaneous low-molecular-weight heparin administration)
- ▶ Clinical context: recent use of heparin (past 7–100 days)
- ▶ Laboratory features: abrupt, potentially reversible fall in platelet count
- ▶ Signs and symptoms
 - Inflammatory: chills, rigours, fever and flushing
 - Cardiorespiratory: tachycardia, hypertension, tachypnoea, dyspnoea, bronchospasm, chest pain or tightness and cardiopulmonary arrest
 - Gastrointestinal: nausea, vomiting and large-volume diarrhoea
 - Neurological: pounding headache, transient global amnesia, transient ischaemic attack or stroke
- ▶ Reprinted with permission from Warkentin and Greinacher.⁶

a secondary humoral response, explain the rapid thrombocytopenia that occurs when patients are re-exposed to heparin.³ All cases have also been found to have antibodies to heparin–PF4 complexes and have tested positive with ELISA. The features of anaphylactoid reactions as reported in various case reports are summarised in table 2.

Of the eight patients reported, all displayed a range of symptoms consistent with anaphylactoid reactions with PF4 antibody positivity. These reactions occurred within 30 min and correlated to a UFH bolus in all patients. It has been quoted, though not published, that patients with anaphylactoid reactions typically present with hypertension (increase from baseline by 30 mm Hg systolic blood pressure). However, from our review, most patients (one had normal vital signs and these were unknown in two patients) were reported to be hypotensive. Similar to our patient, all these reports document an immediate fall in platelet count. Four of the patients suffered cardiopulmonary arrest. Most patients recovered following resuscitation and cessation of heparin (six of eight). Whether a worse outcome is determined by other existing comorbidities, multiple repeated exposures to heparin products, or the severity of platelet decline, is of much interest. The interval of preceding treatment in these patients ranged from 3 to 30 days.

A subset of patients on haemodialysis suffered from HIT-associated anaphylactoid reactions, with documented antibodies and decline in platelet levels. These patients are considered to be particularly high risk due to repeated exposure to heparin and other immunogenic products, thus providing an increased opportunity for contact system activation to develop.⁶ Matsuo and colleagues¹⁴ depicted dyspnoea as the prevalent symptom in seven of eight patients with HIT-associated anaphylactoid reactions on haemodialysis, making it difficult to differentiate from other acute systemic reactions that occur during dialysis. The diagnosis of HIT in patients with myeloproliferative disorders and inherited thrombocytosis is obscured by the finding of platelet count nadirs above or in the normal range, despite a significant drop (30–50%) from baseline platelet count. Risch *et al*¹⁵ reported a case of a patient with essential thrombocytosis who was diagnosed with serologically confirmed HIT despite above-normal platelet counts. Our patient differs in

Table 2 Summary of patients with anaphylactoid reactions following UFH bolus

Author	Age (years)/gender	Pre-exposure, time (anticoagulant)	Relevant findings on previous exposure	Latency (symptom onset after UFH bolus) as reported	Symptoms reported	Outcome	Antibodies to heparin-PF4 complex	Indication for anticoagulation
Mims <i>et al</i> ⁹	53/F	Twice, last 21 days (UFH)	Platelet decline to a nadir of $35 \times 10^9/L$	Immediately	Hypotension, bradycardia, cardiac arrest	Recovered	Positive	Surgery for AV grafting
Mims <i>et al</i> ⁹	70/M	2 months (UFH)	Platelet decline to a nadir of $31 \times 10^9/L$	5 min	Hypotension 60 mm Hg, ventricular tachycardia	Recovered	Positive	Heart transplant
Mims <i>et al</i> ⁹	68/F	Thrice, last 7 days (UFH)	Platelet decline to a nadir of $19 \times 10^9/L$	Immediately	Tachypnoea, dyspnoea, wheezing	Expired	Positive	Haemodialysis
Mims <i>et al</i> ⁹	59/F	1 month (UFH)	None reported	Within minutes	Dyspnoea, tachycardia, hypotension, cardiopulmonary arrest	Recovered	Positive	Deep vein thrombosis
Foreman <i>et al</i> ¹⁰	56/F	14 days (UFH)	None	5 min	Flushing, worsening dyspnoea, hypotension 90 mm Hg, cardiorespiratory arrest	Recovered after extubation	Positive	Pulmonary embolism
Warkentin <i>et al</i> ¹¹	57/M	3 days (LMWH)	Inflammatory (erythematous) skin lesions at injection site	10 min	Chills, rigours, dyspnoea, tachycardia, diaphoresis, headache, tachycardia	Unknown	Positive	Unknown
Teh <i>et al</i> ¹²	57/M	4 days (UFH)	None reported	Within 1 h	Retrograde and anterograde amnesia, normal blood pressure and heart rate	Recovered following heparin cessation	Positive	Mitral valve replacement
Singla <i>et al</i> ¹³	64/M	9 days (LMWH)	Non-necrotising erythematous rash at injection site	10 min	Dyspnoea, flushing, hypotension, VT followed by asystole, new RBBB	Expired	Positive	Suspected deep vein thrombosis

AV, arteriovenous; F, female; LMWH, low-molecular-weight heparin; M, male; RBBB, right bundle branch block; UFH, unfractionated heparin; VT, ventricular tachycardia.

that he belongs to the subset of patients with myeloproliferative disorders with normal platelet counts ($290\text{--}340 \times 10^9/L$).

There have been some cases reported in the literature that patients with heparin exposure who developed thrombocytopenia and signs of thrombosis (such as non-necrotising lesions at the site of subcutaneous injection of UFH or LMWH) developed anaphylactoid reactions with subsequent heparin exposure.^{11 13} However, either due to lack of documentation or lack of recognition of these clinical signs (skin lesions), as related to HIT, these patients received repeated exposure to heparin. Hence, it is important for physicians to promptly recognise these clinical features to prevent subsequent heparin exposure and thereby avoid anaphylactoid reactions. However, it is currently unclear whether this is universally true in all cases.

Case reports of HIT-induced anaphylactoid reactions all convey a similar prolonged, complicated hospital course. The treatment of HIT anaphylactoid reactions is essentially centred on prompt recognition and cessation of heparin products. Therefore, it is vital to correlate the onset of these symptoms with the timing of UFH bolus or infusion, as well as the almost immediate fall in platelet count that ensues. Treatment entails use of an alternative anticoagulant, preferably either argatroban, bivalirudin (direct thrombin inhibitors) or fondaparinux (an

indirect factor Xa inhibitor). Warfarin should not be used in the initial treatment, as it can precipitate warfarin-induced skin necrosis and life-threatening limb gangrene.¹⁶ Platelet

Learning points

- ▶ Heparin-induced thrombocytopenia (HIT)-associated anaphylactoid reactions, although rare, should be considered in the differential diagnosis of a patient who presents with cardiopulmonary arrest soon after receiving a bolus of heparin.
- ▶ Early recognition and prompt therapeutic action in patients with HIT-associated anaphylactoid reaction can prevent further morbidity associated with this unusual but serious condition.
- ▶ The pathogenesis of HIT anaphylactoid reactions appears to be associated with IgG but not IgE.
- ▶ Patients with myeloproliferative disorders who present with thrombotic events and 'normal' platelet counts 5 or more days postcardiac surgery should be evaluated for the possibility of HIT.

transfusions are not recommended unless the bleeding risk is high.¹⁷ Warfarin should be initiated only after platelet counts have recovered (ie, usually to at least $150 \times 10^9/L$). An overlap with non-heparin anticoagulant should be maintained for a minimum of 5 days and until the INR is within the target range over shorter periods of overlap, with continuation of the alternative anticoagulant until the INR values are within therapeutic range.¹⁷

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