CASE REPORT

Bilateral adrenal haemorrhage associated with heparin-induced thrombocytopenia during treatment of Fournier gangrene

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SUMMARY

We present a case of bilateral adrenal haemorrhage (BAH) associated with heparin-induced thrombocytopenia (HIT) in a 61-year-old man admitted to hospital for the treatment of Fournier's gangrene. He presented to hospital with scrotal swelling and fever, and developed spreading erythema and a gangrenous scrotum. His scrotum was surgically debrided and intravenous broad-spectrum antibiotics were administered. Unfractionated heparin was given postoperatively for venous thromboembolism prophylaxis. The patient deteriorated clinically 8–11 days postoperatively with delirium, chest pain and severe hypertension followed by hypotension and thrombocytopenia. Abdominal CT scan revealed bilateral adrenal haemorrhage. Antibodies to the heparin-platelet factor 4 complex were present. HIT-associated BAH was diagnosed and heparin was discontinued. Intravenous bivalirudin and hydrocortisone were started, with rapid improvement in clinical status. BAH is a rare complication of HIT and should be considered in the postoperative patient with unexplained clinical deterioration.

BACKGROUND

Bilateral adrenal haemorrhage (BAH) is a rare complication of heparin-induced thrombocytopenia (HIT). It presents a diagnostic challenge due to its variable clinical presentation, and is often initially diagnosed as sepsis. We present a case of HIT-associated BAH in a patient with Fournier gangrene, a rare necrotising fasciitis of the perineum and scrotum, which can cause sepsis. This case is of interest because of the presentation of HIT-associated BAH mimicking sepsis in a patient with a condition (Fournier gangrene) that can cause sepsis. To our knowledge, this is the first report of BAH in a patient with Fournier gangrene. We believe that this case report will educate clinicians about the importance of considering HIT-associated BAH in postoperative patients with unexplained deterioration in clinical status.

CASE PRESENTATION

A 61-year-old man presented to hospital (day 0) with a 2-day history of scrotal swelling and fever, on a background of type 2 diabetes mellitus. On examination, the scrotum was swollen and erythematous. Sepsis was absent, temperature was 37.9°C, blood pressure 125/65 mm Hg, heart rate 75 bpm and respiratory rate 16 breaths/min. White cell count was elevated ($13.3 \times 10^9/L$). The Uludag Fournier's Gangrene Severity Index¹ (UFGSI) was 2. Initially, scrotal cellulitis was unsuccessfully treated with

intravenous flucloxacillin, and the patient was started on vancomycin, meropenem and lincomycin.

Fournier's gangrene was diagnosed following clinical deterioration and worsening of local symptoms, with surgical emphysema, spreading erythema and a gangrenous right hemiscrotum identified on ultrasound scan. On day 3, sepsis was present, temperature was 39.2°C, blood pressure (BP) 195/94 mm Hg, heart rate 105 bpm, respiratory rate 18 breaths/min and elevated white cell count. The scrotum was surgically debrided twice, with excision of the right hemiscrotum (day 4) followed by excision of necrotic tissue in the left scrotal area (day 5). Scrotal swabs grew *Escherichia coli*.

For venous thromboembolism (VTE) prophylaxis, enoxaparin (40 mg daily) was given for 3 days preoperatively (days 1–3) and unfractionated heparin (5000 units, twice daily) was started after the first operation (day 4), as unfractionated heparin was the VTE prophylaxis agent routinely used by the surgical team. Following surgery, the scrotum healed well and was clean with no evidence of infection. On day 10, the patient developed a diffuse maculopapular erythematous rash affecting predominantly the upper back, torso and buttocks. On day 12, the patient became confused, with severe epigastric pain radiating to the back and systolic BP above 200 mm Hg that was refractory to treatment with four antihypertensive agents. On day 15, the patient remained confused and BP decreased to 100/44. No evidence of infection could be found in the scrotum or other areas, and the patient was afebrile (36.9°C), with a heart rate of 70 bpm, and respiratory rate of 24 breaths/min. The patient did not have nausea, vomiting, abdominal rigidity or rebound tenderness.

INVESTIGATIONS

CT scan of the abdomen on day 13 was unremarkable and showed normal-sized adrenal glands (figure 1). However, a subsequent abdominal CT scan on day 15 revealed bilaterally enlarged, hyperdense adrenal glands, indicating bilateral adrenal haemorrhage (figure 2).

Thrombocytopenia developed rapidly on day 14 with a platelet count of $76 \times 10^9/L$, decreasing from a normal level of $261 \times 10^9/L$ the previous day. White cell count (day 15) was elevated ($16.7 \times 10^9/L$). Blood cultures were negative. Haemoglobin decreased to 90 g/L on day 15, from 105 to 107 g/L on days 10–14. Prothrombin time (PT) was normal. Platelet count continued to

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Figure 1 Abdominal CT scan on postoperative day 9 showing normal adrenal glands.

decline to a nadir of $19 \times 10^9/L$ on postoperative day 16. Antibodies to the heparin-platelet factor 4 complex were detected, confirming the diagnosis of HIT.

TREATMENT

Heparin was immediately ceased (on day 15) and bivalirudin (12.5 mg/h infusion) was initiated and continued for 3 weeks to maintain the activated partial thromboplastin time (aPTT) between 60 and 90 s. Warfarin was initiated, aiming to maintain the internationalised normalised ratio (INR) between 2 and 3. Treatment of adrenal insufficiency was initiated with intravenous hydrocortisone (50 mg, 3 times/day) for three days, followed by oral cortisone acetate (37.5 mg/day).

OUTCOME AND FOLLOW-UP

Rapid improvement in clinical status was observed within 1–2 days following cessation of heparin and initiation of corticosteroid replacement, with BP improving to 125/75, and resolution of the rash and confusion. The patient returned to theatre 2 weeks later (day 32) for scrotal reconstruction with a split-thickness skin graft. He subsequently developed a lower limb deep vein thrombosis and was discharged from hospital (day 47) with warfarin, and oral cortisone for ongoing adrenal insufficiency.

Figure 2 Abdominal CT scan on postoperative day 11 showing bilaterally enlarged, hyperdense adrenal glands, consistent with bilateral adrenal haemorrhage.

DISCUSSION

HIT is a severe autoimmune complication characterised by a rapid decline in platelet levels 5–14 days after heparin exposure.² It is more commonly associated with use of unfractionated heparin (2.6% risk) but can also occur with low-molecular weight heparin (LMWH; 0.2% risk).^{2–3} The pathogenesis of HIT involves binding of heparin to platelet factor 4 (PF4) and formation of heparin-PF4 immunoglobulin G antibodies, leading to activation of platelets, thrombin production and systemic hypercoagulability.^{4–5} Skin lesions occur in 10–20% of patients with HIT.⁶

Thrombosis occurs in up to 50% of patients with HIT and in most cases the thrombi are venous.² Adrenal haemorrhage is a rare complication of HIT and arises from adrenal vein thrombosis leading to outflow obstruction and haemorrhage within the gland.⁷ The risk of adrenal haemorrhage among patients with HIT was 1.6% (2 cases) in a retrospective study of 127 patients with HIT.⁸ In a study of 11 patients with HIT-associated adrenal haemorrhage, 10 cases (91%) of HIT-associated adrenal haemorrhage occurred in the postoperative setting and 10 cases (91%) were bilateral.⁹ Most reported cases of HIT-associated BAH have been in postoperative orthopaedic patients,^{7–9} and orthopaedic surgery increases the risk of thrombotic complications of HIT by an OR of 5.3.¹⁰ BAH can lead to life-threatening adrenal insufficiency and haemodynamic collapse; it is crucial that BAH is promptly recognised and treated.

Diagnosis of BAH is difficult, as the clinical features are variable and non-specific. Signs and symptoms associated with BAH include hypotension, fever, abdominal pain and altered mentation.⁷ Laboratory abnormalities associated with BAH include hypotension, hyperkalaemia and decline in haemoglobin levels or haematocrit.^{7–11} The patient described in this report developed hypotension, abdominal pain, altered mentation and decreased haemoglobin level, but no indication of hyperkalaemia or hyponatraemia.

Septic shock can produce similar clinical features to BAH, and in most reported cases of HIT-associated BAH the initial provisional diagnosis was sepsis.⁷ In this patient, no evidence of infection was found at the time of clinical deterioration, so sepsis was absent, although the criteria for the systemic inflammatory response syndrome¹² were met on day 15. Monitoring of platelet count is important in the postoperative patient, and abrupt (1–2 days) decrease in platelet count is a hallmark of HIT. HIT-associated BAH should be suspected if thrombocytopenia rapidly develops in the postoperative patient with clinical deterioration.

BAH can be caused by sepsis as part of the Waterhouse-Friderichsen syndrome (WFS), which is characterised by petechial rash, coagulopathy, cardiovascular collapse and BAH.¹³ WFS is usually associated with fulminant meningococcaemia, but the syndrome can also be caused by other organisms, including *Streptococcus pneumoniae*, group A β -haemolytic streptococci, *Neisseria gonorrhoeae*, *E. coli*, *Haemophilus influenzae* type b and *Staphylococcus aureus*.^{14–17} WFS is associated with disseminated intravascular coagulation (DIC), a condition in which hypercoagulation and hyperfibrinolysis can lead to consumption of clotting factors and massive haemorrhage.^{18–19} Laboratory findings in DIC include prolonged PT and aPTT, and increased fibrin degradation products (D-dimer).²⁰ In HIT, PT is usually not prolonged and heparin-PF4 antibodies are present.²⁰ We did not assess D-dimer levels, which have been found to be significantly higher in patients with DIC compared to patients with HIT.²¹ In this patient, HIT-associated BAH was diagnosed on the

basis of positive heparin-PF4 antibodies, rapidly developing thrombocytopenia, normal PT and CT findings of BAH.

BAH is usually diagnosed radiologically, with abdominal CT scan showing hyperdense enlarged adrenal glands.⁹ Non-contrast CT is adequate for diagnosis of adrenal haemorrhage.²² Ultrasonography is the modality of choice for imaging adrenal haemorrhage in infants and MRI is useful for determining the age of an adrenal haemorrhage.²³ Adrenal insufficiency due to BAH can be confirmed by the corticotropin stimulation test, in which 250 µg of cosyntropin (synthetic corticotropin) is administered intramuscularly or intravenously, and the plasma cortisol levels are measured at 0, 30 and 60 min after administration.²⁴ Adrenal insufficiency is present if the rise in cortisol level from baseline to the peak value (at 30 or 60 min) is less than 9 µg/dL. Low serum cortisol (below 15 µg/dL) is also a marker of adrenal insufficiency.

Fournier's gangrene is a necrotising fasciitis of the perineum that often involves the scrotum and is associated with diabetes mellitus in 50% of cases.^{25 26} The aetiology is usually polymicrobial and *E. coli* is the most frequently identified organism.^{25 26} The pathophysiology of Fournier gangrene involves synergism between aerobic and anaerobic bacteria.²⁵ There are several mechanisms by which synergism may occur, including the provision of essential nutrients by one microbe to another microbe, inhibition of leucocyte phagocytosis of aerobes by anaerobes and decrease in oxygen tension by aerobes, creating an optimal environment for anaerobes.^{27 28} Sepsis has been reported in 26% of cases in a study of 35 patients with Fournier's gangrene, and is associated with a high-mortality rate.²⁶ Treatment of Fournier's gangrene should be prompt and aggressive, with early surgical debridement and broad spectrum antibiotics.^{25 26}

Treatment of HIT requires discontinuation of heparin and initiation of an alternative anticoagulant to reduce the risk of thrombosis associated with HIT.² Parenteral direct thrombin inhibitors, including argatroban, desirudin and bivalirudin, have been widely used in the management of HIT.^{29 30} The choice of anticoagulant agent and the dose should take into account comorbidities such as renal and hepatic impairment.^{29 30}

Treatment of BAH is aimed at resolving adrenal insufficiency by administration of corticosteroids. For management of acute adrenal insufficiency, it is recommended to give 100–200 mg/day of hydrocortisone intravenously in four divided doses.^{31 32} For long-term treatment of adrenal insufficiency, oral hydrocortisone (15–25 mg/day) or cortisone acetate (25–37.5 mg/day) is indicated.³³

To our knowledge, this is the first reported case of HIT-associated BAH in a patient with Fournier gangrene. The

majority of cases of HIT-associated BAH have occurred following orthopaedic surgery, and there is only one previously reported case following a urological procedure.^{7 9 34} It is imperative that HIT-associated BAH is considered as a potential cause of unexplained pain, fever or haemodynamic compromise in all patients exposed to heparin.

Contributors TLT wrote the first draft of the manuscript. IAT and JR were involved in patient care. All authors revised and edited the manuscript and approved the final manuscript.

Competing interests None.

Patient consent Obtained.

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Learning points

- Consider the possibility of heparin-induced thrombocytopenia (HIT) in all patients exposed to heparin.
- Unexplained hypotension, fever, pain or confusion may be caused by bilateral adrenal haemorrhage (BAH) associated with HIT.
- Monitoring of platelet count is important because thrombocytopenia can be a key differentiator between sepsis and HIT-associated BAH.
- Treatment of HIT-associated BAH requires discontinuation of heparin, initiation of alternative anticoagulation and corticosteroid replacement.

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