CASE REPORT

Bilateral adrenal haemorrhagic infarction in a patient with antiphospholipid syndrome

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SUMMARY

A 68-year-old woman with antiphospholipid syndrome presented with a 3-day history of bilateral loin pain, vomiting, fever and confusion. On examination she was febrile, hypotensive and tachycardic. Investigations revealed raised inflammatory markers, renal impairment and hyponatraemia. Abdominal ultrasound revealed two well-defined heterogeneous areas bilaterally in the region of the adrenal glands. This prompted serum cortisol measurement and a CT of the abdomen. Cortisol was low in the context of sepsis at 48 nmol/L, and CT confirmed bilateral heterogeneous adrenal pathology. The patient was managed for septic shock and adrenal insufficiency. She was recognised to have several risk factors for haemorrhagic infarction of the adrenals: antiphospholipid syndrome, sepsis, postoperative state and anticoagulant therapy. She was discharged well on glucocorticoid and mineralocorticoid therapy and a repeat CT at 4 weeks confirmed the diagnosis of bilateral adrenal infarct and haemorrhage.

BACKGROUND

This patient demonstrated classic clinical features of haemorrhagic infarction of the adrenals, and presented with several well-recognised risk factors. The case highlights the difficulty in recognising adrenal crisis in the context of sepsis, and the diagnostic value in CT alongside careful interpretation of serum cortisol.

CASE PRESENTATION

A 68-year-old woman with a history of antiphospholipid syndrome and hypertension presented to A&E with a 3-day history of worsening bilateral loin pain, vomiting, fever and confusion. Her regular prescriptions were warfarin (target international normalised ratio (INR) range 3.5–4), atenolol and bendroflumethiazide. The bilateral loin pain developed initially over a 1 h period, and was described as a severe constant ‘indigestion-like’ pain, which progressed up her back over the first day. She noticed it less over the second and third day of pain, but became increasingly confused. The pain was 9/10 in severity and unaffected by oral paracetamol. She vomited throughout this 3-day period, and was unable to retain any food or fluids. There was no haematemesis. She described feeling cold and sweaty, and recalled thinking that her appearance was unusually pale, with a grey tinge to her skin. She denied urinary symptoms and described constipation, with no bowel movements for roughly 1 week preceding admission. She denied weight loss, respiratory symptoms, chest

pain or headache. She had not noticed any breaks in the skin, rashes or bruising.

Seven days prior to the onset of her symptoms, the patient had been discharged well following a right total hip replacement for osteoarthritis. On day 2 of her symptoms, a general practitioner (GP) visited the patient at home. Finding her to be febrile, the GP gave her a stat dose of nitrofurantoin.

On presentation to A&E, she was pale and sweaty with a temperature of 38.2°C and cold peripheries. She was tachycardic (HR: 129 bpm regular) and hypotensive (BP: 82/52 mm Hg). Glasgow Coma Scale was 14/15 (confusion). Her abdomen was soft and non-tender and there were no masses or organomegaly. No renal angle tenderness was documented. The site of the total hip replacement was unremarkable, with no sign of infection, and no other breaks in the skin, or rashes or bruising. Cardiac and respiratory examinations were unremarkable.

INVESTIGATIONS

An arterial blood gas on admission revealed metabolic alkalosis (pH 7.56) and hypoxia (PO₂ 7.4), with a lactate of 1.3 mmol/L. Blood tests revealed raised inflammatory markers (C reactive protein 194 mg/L, white cell count 17.1×10⁹/L), impaired renal function (urea 8.6 mmol/L, creatinine 167 µmol/L; creatinine 83 µmol/L 1 month previously) and globally deranged liver function tests (bilirubin 29 µmol/L, alkaline phosphatase 220 iU/L, alanine transaminase 71 iU/L), with INR 4.6 (target 3.5–4). Amylase was within normal range (56 IU/L).

Figure 1 CT scan demonstrating bilateral adrenal masses and surrounding inflammatory/infiltrative opacities.

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Figure 2 Sepsis six (ABG, arterial blood gas; BP, blood pressure; FBC, full blood count; LFT, liver function test; MSU, mid-stream urine; U&E, urea and electrolytes; IV, intravenous).

1: Oxygen	<ul style="list-style-type: none"> •15 L/min via non-rebreath mask + reservoir bag •target saturation: 100%
2: IV fluid bolus	<ul style="list-style-type: none"> •500-1000ml bolus of Hartman's •[increase if systolic BP<90 or lactate >4]
3: Blood cultures	<ul style="list-style-type: none"> •[negative]
4: Antibiotics	<ul style="list-style-type: none"> •empirical < 1hr [→ Tazocin + Gentamicin given] •microbiology guided [targeted / stepped-down] → Tazocin + Gentamicin continued
5: Lactate + bloods	<ul style="list-style-type: none"> •ABG •FBC, U&E, LFT, clotting, glucose
6: Monitor urine output	<ul style="list-style-type: none"> •monitor output hourly [catheter inserted] •urine dip & MSU - send for microscopy, culture + sensitivity

The patient was also hyponatraemic (Na 132 mmol/L) and hypokalaemic (K 2.4 mmol/L). Urine dipstick revealed 2+ blood, and was otherwise unremarkable. Blood glucose was 7.5 mmol/L. Blood and urine cultures were negative.

ECG, chest X-ray and echocardiogram were unremarkable. Cortisol was extremely low in the context of sepsis at 48 nmol/L, and abdominal ultrasound revealed two well-defined heterogeneous areas bilaterally in the adrenal gland region. CT scan confirmed bilateral heterogeneous adrenal pathology (figure 1).

DIFFERENTIAL DIAGNOSIS

Raised inflammatory markers and fever suggested an underlying sepsis, with an acute presentation of adrenal insufficiency indicated by low serum cortisol and sodium, and a strong suspicion of adrenal pathology on imaging. Low potassium could be explained by thiazide diuretic use and repeated vomiting. Concurrent sepsis and adrenal insufficiency resulted in profound hypotension.

Figure 3 Follow-up CT scan at 4 weeks consistent with resolving bilateral adrenal infarct and haemorrhage.

Possible causes of this patient's adrenal insufficiency include:

- Bilateral acute adrenal infarct and haemorrhage:
 - Risk factors included warfarin treatment but also the underlying hypercoagulable state (ie, antiphospholipid syndrome), sepsis and the postoperative state.^{1 2}
- Stress precipitating acute crisis in the context of undiagnosed chronic adrenal insufficiency:
 - This possibility seemed less likely as the patient had not previously reported malaise, anorexia, weight loss or hyperpigmentation and had recently undergone major surgery without mishap.^{3–7}

TREATMENT

Initial management followed national guidelines for sepsis ('Sepsis Six') (figure 2).⁸

Adrenal insufficiency was diagnosed and high-dose intravenous hydrocortisone (100 mg every 6 h) started alongside careful fluid resuscitation. This was tapered over 3 days to oral maintenance with hydrocortisone and fludrocortisone as the patient improved. She was discharged with a plan for repeat CT of the abdomen. No focal source of infection was identified.

OUTCOME AND FOLLOW-UP

Repeat CT of the abdomen 4 weeks later (figure 3).

Imaging is consistent with resolving bilateral adrenal infarct and haemorrhage. A splenic infarct is also apparent on CT.

Figure 4 Hypothesised pathogenesis of haemorrhagic infarction of the adrenals in sepsis (ACTH, adrenocorticotropic hormone).

Figure 5 Clinical presentation of haemorrhagic infarction of the adrenals.

Figure 6 Risk factors for haemorrhagic infarction of the adrenals.

	Anticoagulant therapy	Although haemorrhagic adrenal infarction is usually within the first 2-12 days of anticoagulant therapy
	Hypercoagulable states such as antiphospholipid syndrome	Clotting test results usually within normal range Spontaneous bleeding elsewhere is usually not evident
	The post-operative state	
	Sepsis	
	Any cause of severe stress	
	Thromboembolic Dx	

DISCUSSION

Acute adrenal insufficiency is most common in the context of long-term steroid use and adrenal atrophy. In the absence of long-term steroid use, acute adrenal crisis is usually caused by primary adrenal failure. It is rare for pituitary disease to present with an acute adrenal crisis, as the mineralocorticoid axis remains intact, and cardiovascular compromise is therefore rare.

Haemorrhagic infarction of the adrenals most commonly occurs in the context of sepsis^{1 2 9}; this is referred to as Waterhouse-Friderichsen syndrome.¹⁰ Pathogenesis is unclear, although a causal mechanism is hypothesised (figure 4).¹

Meningococcaemia is the most common culprit,¹⁰ however, other pathogens have been found to precipitate haemorrhagic infarction (including *Pseudomonas aeruginosa*,¹¹ *Streptococcus pneumoniae*, *Neisseria gonorrhoeae*, *Escherichia coli*, *Haemophilus influenzae*, *Staphylococcus aureus*).¹ The typical clinical presentation closely correlates with how this patient presented (figure 5).²

There is considerable overlap between the clinical presentation of sepsis and acute adrenal insufficiency, and the difficulty in establishing an early diagnosis is well-recognised in the literature.¹ These patients are often critically unwell and prompt diagnosis is essential for appropriate management. Haemorrhagic infarction of the adrenals is often multifactorial and patients often present with risk factors. Typical risk factors closely align with this case (figure 6).^{1 2}

Care must be taken with interpreting serum cortisol.^{12 13} In the context of severe sepsis, cortisol measurement within 'normal range' can still indicate a relative insufficiency. Alongside risk factor recognition, case reports frequently identify imaging as an important diagnostic turning point.¹ Prior to the availability of CT, the diagnosis of haemorrhagic infarction of the adrenals was usually made at autopsy.⁹

Patients with adrenal infarct and haemorrhage may recover adrenal function months later.¹⁴ The availability of an effective

diagnostic tool and the potential for full recovery necessitate vigilance in the setting of hypotensive sepsis, with a low threshold for CT in patients with risk factors for haemorrhagic infarction of the adrenals.

Learning points

- ▶ Acute adrenal insufficiency presents non-specifically and can mimic septic shock.
- ▶ The diagnosis should be considered in septic patients with risk factors such as antiphospholipid syndrome.
- ▶ Interestingly, patients with antiphospholipid syndrome may present with normal clotting tests and without signs of spontaneous bleeding.
- ▶ CT scan is the most useful diagnostic tool, and care should be taken in interpreting serum cortisol in acutely unwell patients.

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Competing interests None.

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Reminder of important clinical lesson

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