An unusual cause of adrenal insufficiency and bilateral adrenal masses

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Summary

Primary adrenal insufficiency secondary to syphilis is extremely rare, with only five cases being reported in the literature. We report a case of adrenal insufficiency as a manifestation of Treponema pallidum infection (tertiary syphilis). A 69-year-old, previously fit and well Caucasian male was found to have adrenal insufficiency after being admitted with weight loss, anorexia and postural dizziness resulting in a fall. Biochemical testing showed hyponatraemia, hyperkalaemia, and an inadequate response to Synacthen testing, with a peak cortisol level of 302 nmol/L after administration of 250 µg Synacthen. Abdominal imaging revealed bilateral adrenal hyperplasia with inguinal and retroperitoneal lymphadenopathy. He was started on hydrocortisone replacement; however, it was not until he re-attended ophthalmology with a red eye and visual loss 1 month later, that further work-up revealed the diagnosis of tertiary syphilis. Following a course of penicillin, repeat imaging 5 months later showed resolution of the abnormal radiological appearances. However, adrenal function has not recovered and 3 years following initial presentation, the patient remains on both glucocorticoid and mineralocorticoid replacement. In conclusion, this case highlights the importance of considering syphilis as a potential differential diagnosis in patients presenting with adrenal insufficiency and bilateral adrenal masses, given the recent re-emergence of this condition. The relative ease of treating infectious causes of adrenal lesions makes accurate and timely diagnosis crucial.

Learning points:

- Infectious causes, including syphilis, should be excluded before considering adrenalectomy or biopsy for any patient presenting with an adrenal mass.
- It is important to perform a full infection screen including tests for human immunodeficiency virus, other blood-borne viruses and concurrent sexually transmitted diseases in patients presenting with bilateral adrenal hyperplasia with primary adrenal insufficiency.
- Awareness of syphilis as a potential differential diagnosis is important, as it not only has a wide range of clinical presentations, but its prevalence has been increasing in recent times.

Background

Adrenal insufficiency, a life-threatening disorder first described by Thomas Addison in 1855, is characterised by deficient production of the adrenal corticosteroids including glucocorticoids and mineralocorticoids, which are essential for life. Underlying pathology may be present in the adrenal cortex (primary adrenal insufficiency), anterior pituitary gland or hypothalamus (secondary). Tertiary adrenal insufficiency may result from exogenous suppression of adrenocorticotropic hormone (ACTH), for example by inhaled or oral corticosteroid use. Classical
symptoms of adrenal insufficiency include weakness, anorexia, abdominal pain, orthostatic hypotension and in primary adrenal insufficiency, skin hyperpigmentation.

**Case presentation**

A 69-year-old, previously fit and well Caucasian male was admitted with weight loss, anorexia and postural dizziness resulting in a fall. He had been diagnosed with psoriasis 2 months prior to admission, after developing a rash on his scalp and hands. He had a 40 pack-year smoking history. He was using topical ketoconazole shampoo but was not on any other regular medication. There was no history of corticosteroid use. On physical examination, finger clubbing and mild skin pigmentation were present. He had orthostatic hypotension – blood pressure was 117/70 mmHg lying; and 95/60 mmHg sitting. He was aphyrexic, and systemic examination was otherwise unremarkable.

**Investigation**

Initial investigations showed hyponatraemia (sodium: 126 mmol/L), hyperkalaemia (potassium: 5.7 mmol/L) and acute kidney injury (urea: 17.4 mmol/L, creatinine: 186 µmol/L with a baseline creatinine of 70 µmol/L). He also had a normocytic anaemia (haemoglobin: 110 g/L, MCV: 85 f/L) with raised inflammatory markers (C-reactive protein (CRP): 66 mg/L) but normal white cell count (WCC) (8.90 × 10⁹/L, range: 4–11 × 10⁹/L) and neutrophil count (4.80 × 10⁹/L, range: 2–7 × 10⁹/L). Adjusted calcium and thyroid-stimulating hormone (TSH) were within the reference range. Alkaline phosphatase (ALP) was raised at 216 U/L (30–130) with normal alanine aminotransferase (ALT) of 12 U/L (0–40). Tumour markers including alpha-fetoprotein, Ca 19-9 and carcinoembryonic antigen (CEA) were negative.

Urine culture was positive for *Staphylococcus aureus*, while a plain chest X-ray showed bilateral apical scarring but no evidence of active infection. Tests for tuberculosis (QuantiFERON-TB Gold Test, AFB smear and culture for *Mycobacterium*) were negative. He was commenced on oral cephalexin for a urinary tract infection as he had symptoms of nocturia and reduced flow.

During admission, the patient developed worsening hyponatraemia, with serum sodium dropping to 120 mmol/L by day 5 of admission. CRP had improved from 66 mg/L to 42 mg/L, WCC remained within normal limits (5.8 × 10⁹/L) and renal function had improved approaching baseline (urea: 4.2 mmol/L, creatinine: 86 µmol/L). Serum osmolality was 253 mmol/kg, paired urine osmolality: 402 mmol/kg, urine sodium: 123 mmol/L and urine potassium: 19 mmol/L. 09:00 h cortisol was low at 290 nmol/L (Roche E170 Generation I assay, 09:00 h reference range ≥400 nmol/L) and a repeat morning cortisol was 275 nmol/L, rising to 302 nmol/L 60 min following administration of 250 µg of Synacthen (tetracosactide; ACTH: 1–24; reference response >550 nmol/L).

In the context of adrenal insufficiency, plasma ACTH was measured and found to be elevated at 373 ng/L (normal range: 0–47), indicating primary adrenal insufficiency. 17-Alphahydroxyprogesterone was within reference range. Renin was 22 mIU/L (<59.7 mIU/L, supine); aldosterone was <103 pmol/L (104–450 pmol/L).

CT thorax, abdomen and pelvis was performed on admission to investigate for possible malignancy, in view of symptoms of weight loss, hyponatraemia and anorexia. This showed bilateral diffusely enlarged adrenal glands, which showed heterogeneous enhancement (Fig. 1). It also confirmed the presence of apical scarring in both lungs, several poorly defined foci in the liver and apparent bladder wall thickening. Of note, there was also inguinal and retroperitoneal lymphadenopathy. The above liver and adrenal findings were then confirmed in an abdominal MRI (Fig. 2).

**Re-presentation and diagnosis**

One month after his initial hospital admission, the patient presented to our ophthalmology emergency department with a week’s history of a red left eye associated with reduced visual acuity and floaters. Examination showed bilateral uveitis, worse on the left and no retinitis. On further questioning, he also admitted to having a creamy genital discharge for the past 3 weeks. There were no mouth or genital ulcers.

**Treatment**

The patient was commenced on oral hydrocortisone (20 mg on waking, 10 mg in the afternoon) during his initial hospital admission and was discharged home on the following doses: 10 mg on waking, 10 mg at noon and 5 mg in the afternoon. Ketoconazole shampoo was stopped.

Following the diagnosis of syphilis, he received 1.9 g intravenous benzylpenicillin 4 hourly for 17 days, followed by a single dose of 2.4 g procaine benzylpenicillin intramuscularly on discharge.
Outcome and follow-up

Repeat MRI abdomen 5 months following initial presentation showed normal adrenal gland appearances and resolution of the non-specific liver lesions (Fig. 2, panels C and D). Serological tests showed a continual decrease in rapid plasma reagin titres (1:32 at 6 months; 1:2 at 16 months), confirming good response to treatment.

Repeat short Synacthen testing was done 5 months after initial antibiotic treatment, showing inadequate response (peak cortisol 316 at 30min; Roche E170 Generation I assay, 09:00h reference range >550 nmol/L), indicating ongoing adrenal insufficiency. Two years after his initial presentation, adrenal cell antibodies, assayed by indirect immunofluorescence (using Bio-Diagnostics Limited slides and Dako rabbit anti-human IgG fluorescein isothiocyanate conjugate), were reported as positive.

Presently, 3 years after initial presentation, the patient remains on twice-daily oral hydrocortisone (10mg on waking, 5mg at noon) and fludrocortisone 50µg daily.

Discussion

A range of conditions could potentially cause adrenal insufficiency with bilateral adrenal hyperplasia (Table 1). Infections caused by various other organisms can also lead to adrenal insufficiency, but do not typically lead to bilateral adrenal masses – these include CMV, HSV and Pneumocystis carinii among others.

Adrenal insufficiency due to tertiary syphilis is rare; and only five case reports have been published thus far – in New Zealand (2012) (1), Netherlands (2012) (2), Japan (1966) (3), Portugal (1954) (4) and the United Kingdom (UK) (1934) (5). To our knowledge, this is the first case described in the UK in more than eight decades.

Syphilis is a curable, sexually transmitted infection caused by a bacterial infection with Treponema pallidum. If left untreated, it progresses through four key stages: primary (chancre, regional lymphadenopathy), secondary (skin rashes, generalised lymphadenopathy), latent (absence of symptoms) and tertiary (gummas,
Syphilis is a re-emerging disease, with an estimated 11 million new cases occurring globally among adults aged 15–49 years (7). Recent data from Public Health England shows the number of cases of syphilis in England have reached its highest level since 1949. A total of 5920 cases were diagnosed in 2016, a 12% increase from 2015, and a 97% increase since 2012 (8). The vast majority of patients were males (94%), and men who have sex with men accounted for 79.4%. With this epidemiological trend, it is increasingly important to consider syphilis as a differential diagnosis in patients with acute adrenal insufficiency as we may possibly see a growing number of patients with untreated tertiary syphilis in the coming years. This may present in a number of ways – gummatous syphilis (granulomatous lesions in various organs); cardiovascular complications or tertiary syphilis, like in our patient.

There were two missed opportunities to diagnose syphilis in this patient, before he presented with uveitis, which led to the syphilis serology being taken. Firstly, when he presented with palmar lesions diagnosed as ‘psoriasis’ (which in retrospect, was likely a manifestation of secondary syphilis), and then when he presented with adrenal insufficiency and bilateral adrenal masses. Our assumption was that the imaging appearances were due to malignant adrenal infiltration, possibly with a urological primary site, given his bladder symptoms and abnormal imaging. Infectious causes of adrenal infiltration were not seriously considered initially, despite his raised serum CRP concentration.

We expected the patient's adrenal function to recover following treatment of syphilis, in keeping with the resolution of radiological abnormalities. However, this was not the case even 3 years following presentation and therefore adrenal antibodies were measured at this point. We suspect that in this case, adrenocortical antigen release secondary to infectious adrenal destruction may have triggered the anti-adrenal immune response. This is in contrast to a previous case report which describes recovery of adrenal function following treatment of syphilis (1).

We would like to highlight the importance of recognising and diagnosing reversible causes of adrenal lesions to prevent potentially inappropriate surgical intervention. There have been case reports of resected adrenal tumours turning out to be gummatous syphilis (2) or infectious hepatic lesions diagnosed mistakenly as metastases.

In conclusion, this case clearly illustrates the potential diagnostic challenge that syphilis is well known for. The relative ease of treating infectious causes of adrenal lesions makes accurate and timely diagnosis crucial.

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Table 1  Differential diagnosis of adrenal insufficiency and bilateral adrenal hyperplasia.

| Causes of adrenal insufficiency and bilateral adrenal hyperplasia |
|---------------------------------------------------------------|
| Congenital                                                                 |
| Malignancy                                                                 |
| Infections                                                                 |
| Infiltrative disease                                                |
| Vascular                                                         |
| Congenital adrenal hyperplasia                                      |
| Adrenal metastases                                                |
| Primary bilateral adrenal lymphoma                                 |
| TB, syphilis, histoplasmosis                                        |
| Blastomycosis                                                    |
| Paracoccidioidomycosis                                            |
| Amyloidosis                                                       |
| Haemochromatosis                                                  |
| Adrenal haemorrhage or acute infarction i.e. Waterhouse-Friedrickson syndrome, antiphospholipid (Hughes) syndrome |

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Cardiovascular and neurological symptoms) (6). Syphilis can potentially affect many organs in the body and thus can present a diagnostic challenge to physicians. The father of modern medicine, Sir William Osler once said ‘he who knows syphilis knows medicine’, and indeed an entire medical subspecialty – syphilology – was developed in the 19th century devoted to the study of this ‘great mimic’.

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Declaration of interest
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Patient consent
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Author contribution statement
Dr S A Tee wrote the first draft and is involved in ongoing follow-up, Drs E H Gan, M Z Kanaan and D A Price were involved in the initial investigation and care of the patient; Dr T Hoare reported the radiological images and Prof. S H S Pearce supervised the initial management and ongoing follow-up of the patient.
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