

Lessons from practice

The not-so-natural herb: a case of exogenous Cushing syndrome

Clinical record

A 44-year-old man presented to the emergency department with one month of worsening breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, and pitting oedema to the thighs. Past medical history included hypertension, dyslipidaemia, and tophaceous gout. His regular medications were perindopril, amlodipine, atorvastatin and frusemide. On examination, his blood pressure was 189/99 mmHg and oxygen saturation was 90% on room air. The patient had cushingoid features such as dorsocervical fat pad, livid abdominal striae, and moon facies. His investigations included chest x-ray showing pulmonary congestion; transthoracic echocardiogram demonstrating diastolic dysfunction, with preserved ejection fraction of 55%; and normal urinary protein, with creatinine ratio and liver screens not suggestive of cirrhosis. Blood tests showed undetectable morning cortisol (< 10 nmol/L; reference interval [RI], 200–650 nmol/L), low adrenocorticotrophic hormone (ACTH; < 5 ng/L; RI, 10–50 ng/L) and low urinary free cortisol (13 nmol/d; RI, 10–165 nmol/d). It was suspected the patient had secondary adrenal insufficiency from exogenous glucocorticoid use. However, both the general practitioner and the patient denied any recent glucocorticoid use.

Further pituitary testing showed preserved thyroid function, normal growth hormone, marginally elevated prolactin (426 mU/L; RI, 56–278 mU/L) and low testosterone (3.1 nmol/L; RI, 9–35 nmol/L) with normal luteinising hormone and follicle-stimulating hormone. The gonadal axis changes were attributed to chronic illness. An overnight metyrapone stimulation test was done to assess his hypothalamic–pituitary–adrenal (HPA) axis.¹ Cortisol synthesis in the adrenal gland involves the conversion of 11-deoxycortisol to cortisol via the enzyme 11 β -hydroxylase (CYP11 β -1). Metyrapone inhibits CYP11 β -1 causing a cortisol deficient state. The lack of cortisol feedback to the pituitary and hypothalamus leads to a rise in corticotropin-releasing hormone and ACTH.² In a patient with an intact HPA axis, an increase in 11-deoxycortisol (> 200 nmol/L) with low cortisol (< 138 nmol/L) is expected. The patient had an abnormal overnight metyrapone stimulation test, with low cortisol (< 10 nmol/L) and low 11-deoxycortisol (0.8 nmol/L) confirming the diagnosis of adrenal insufficiency. Magnetic resonance imaging scan of the pituitary gland was attempted but not tolerated. Exogenous glucocorticoid use remained a possible differential diagnosis. The patient later revealed that, for five months, he had taken a herbal medicine for gout, introduced to him by a friend.

The herbal medication *Nhan Sam Tuyet Lien* was sent to a chemical pathology laboratory to assess its glucocorticoid potential. The presence of dexamethasone was confirmed using liquid chromatography tandem mass spectrometry (Supporting Information). The patient had been taking four tablets a day, equivalent to about 1.4 mg of dexamethasone per day. The presence of dexamethasone was not disclosed on the medication's ingredient list (Box).

In summary, this patient had Cushing syndrome secondary to exogenous glucocorticoid use. He was unknowingly taking a herbal medication containing dexamethasone, frusemide and chlorpheniramine. After the cessation of this medication and commencing a physiological dose of prednisone, the patient lost 10 kg and both his oedema and hypertension improved. This case highlights the importance of history taking for complementary and alternative medicines.

The herbal medicine was reported to the Australian Therapeutic Goods Administration through the Adverse Event Reporting section on its website.

Discussion

Exogenous long term glucocorticoid use is the most common cause of Cushing syndrome. Contributing factors include the type of synthetic glucocorticoid used, its potency and half-life, duration of use, dose prescribed, and the patient's body mass index. The metabolic consequences of exogenous Cushing syndrome take weeks to months to develop with a supraphysiological dose of glucocorticoid. Glucocorticoids in supraphysiological doses have mineralocorticoid-like effects, promoting salt and water retention and exacerbating hypertension.

Indications, instructions and ingredients listed on the herbal product packaging

Indications: Lumbago, gout, arthrodynia, myasthenia, limb numbness, pain induced by acclimation fever and rheumatism, osteoscopy, and arthritis

Instructions: Two pills two to three times per day, taken with warm water after meals

Ingredients:

- Ginseng 10 mg
- Rhizoma *Atractylodis* 20 mg
- *Campanumaea pilosula* 20 mg
- *Radix angelicae sinensis* 12 mg
- *Radix angelicae tuho* 10 mg
- *Herba distanthe* 8 mg
- *Cortex eucommiae* 10 mg
- *Fructus lycii* 7 mg
- *Radix Paeoniae Alba* 13 mg

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The complexity of managing exogenous Cushing syndrome lies in the underlying risk of glucocorticoid-induced adrenal insufficiency from suppressed endogenous ACTH and cortisol production. Glucocorticoid medications exert negative feedback on the HPA axis, and extended use of these causes adrenal cortical atrophy, specifically of the zona fasciculata and zona reticularis involved in glucocorticoid and androgen production respectively.³

Diagnosis of adrenal insufficiency requires demonstration of inappropriately low cortisol secretion. A paired measurement of ACTH with low cortisol will usually indicate whether the adrenal insufficiency is primary (ACTH elevated) or secondary (ACTH low or inappropriately normal). A low morning cortisol (<140 nmol/L) strongly suggests adrenal insufficiency. However, dynamic tests are often required for diagnosis of adrenal insufficiency. The short synacthen test is often used to assess adrenal function but does not test ACTH secretory reserve. The insulin tolerance test remains the gold standard test for examining the HPA axis, including ACTH reserve, but this test has many drawbacks.^{4,5} The overnight metyrapone stimulation test is an alternative to the insulin tolerance test and is more easily performed.

Although life-threatening acute adrenal insufficiency occurs most commonly in primary adrenal insufficiency (Addison disease), it can also occur in patients with glucocorticoid-induced adrenal insufficiency (secondary adrenal insufficiency), typically precipitated by abrupt glucocorticoid cessation or intercurrent illness.⁶ Once the diagnosis of glucocorticoid-induced adrenal insufficiency is established, slow tapering of glucocorticoid from a physiological dose is required to avoid precipitation of acute adrenal insufficiency. This process can typically take months to achieve.⁷

A recent publication⁸ also warned about the dangers of the herbal medicine that our patient was taking. The article reported the varied presentation of exogenous Cushing syndrome, including acute adrenal insufficiency, severe hyponatraemia, and resistant hypertension.

Since January 2022, the Therapeutic Goods Administration and New Zealand Medsafe have published warnings to alert consumers to the danger of this product.^{9,10} The United States Food and Drug Administration has reported another medicine with glucocorticoid adulteration, *Artri Ajo King*, with some cases being fatal.¹¹

Supporting Information

Additional Supporting Information is included with the online version of this article.

Lessons from practice

- When taking a medication history, complementary and alternative medicines need to be reviewed because they may have undisclosed ingredients, since herbs and dietary supplements are not subject to regulatory scrutiny. These medications can have profound impacts on the patient's health and wellbeing.
- If there are concerns regarding undisclosed ingredients within complementary and alternative medicines affecting a patient's health, it is best to contact the local pharmacist and chemical pathology laboratory to evaluate the active ingredients within.
- Biochemical hypoadrenalism with clinical signs of Cushing syndrome should herald the possibility of exogenous glucocorticoid use.
- Glucocorticoid-induced adrenal insufficiency can present in many ways, including life-threatening acute adrenal crisis.

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