

ENDGAMES

CASE REPORT

A difficult case of atopic eczema

Giorgia L Garrett *foundation year 2 doctor*¹, Joseph Benjamin Davies *radiology specialty trainee*², Pamela Terezinha Fiandeiro *dermatology specialty trainee*³, Catherine H Smith *professor of dermatology and therapeutics*⁴

¹Lewisham Hospital NHS Trust, University Hospital Lewisham, London, UK; ²Department of Radiology, Barts Health NHS Trust, London, UK;

³Department of Dermatology, King's College Hospital NHS Trust, London, UK; ⁴Skin Therapy Research Unit, St John's Institute of Dermatology, St Thomas' Hospital NHS Trust, London, UK

A 56 year old retired administrator was referred to the dermatology department for a second opinion on the management of lifelong atopic dermatitis. She had been applying 1% hydrocortisone cream to her face and betamethasone valerate ointment to her body twice daily for 10 years. She also had allergic asthma, which had been controlled with beclomethasone dipropionate inhaler 400 µg twice daily for 11 years, and she had been prescribed 12 courses of oral prednisolone (average dose 30 mg daily for five days) for flare-ups of both eczema and asthma.

On examination she had generalised atopic dermatitis as well as facial telangiectasias and plethora, truncal obesity, and striae in the axillary folds and groins with cutaneous atrophy and spontaneous bruising. Investigations showed a baseline cortisol of 9 nmol/L (reference range 171-536 nmol/L at 7 am to 9 am) and an undetectable baseline adrenocorticotrophic hormone of <5 pmol/L (<46 pmol/L at 9 am), with a peak cortisol of 137 nmol/L after 60 minutes of 250 µg intravenous tetracosactide (synacthen) (expected result ≥500 nmol/L). Impaired glucose tolerance and osteopenia were also diagnosed (spinal dual energy x ray absorptiometry T score -1.9).

Azathioprine, an immunosuppressant and steroid sparing agent, was started and endocrinology input resulted in a programme of slow steroid weaning. Although her eczema improved, she developed weakness, hypotension, and diarrhoea, which limited her daily activities.

Questions

- 1 What is the diagnosis based on these findings?
- 2 What is the most likely cause of this condition?
- 3 Why did the patient develop fatigue, postural hypotension, and diarrhoea after weaning off treatment?
- 4 What clinical strategies can be used to minimise systemic absorption of topical steroids in atopic eczema?

Answers

1 What is the diagnosis based on these findings?

Short answer

The history, examination, and laboratory findings are consistent with a diagnosis of iatrogenic Cushing's syndrome.

Long answer

Systemic absorption of long term exogenous glucocorticoids can induce iatrogenic Cushing's syndrome. Our patient had a cushingoid appearance, with signs of cutaneous and systemic steroid toxicity (figs 1 and 2).

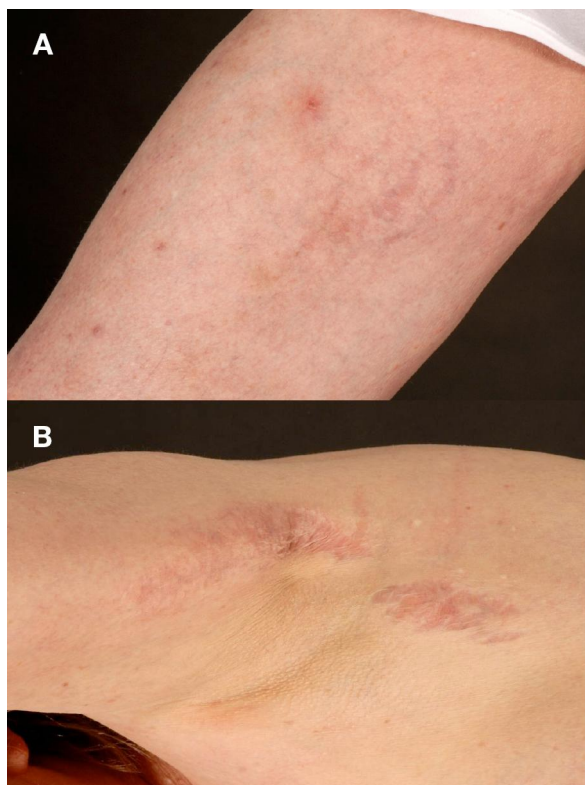


Fig 1 Cutaneous and systemic adverse effects of steroid treatment. (A) Striae in the axillary folds; (B) striae in the antecubital fossae



Fig 2 Steroid associated adverse effects on the face: telangiectasias and moon facies

Complications of excess circulating corticosteroids include osteoporosis, mood disturbance, oligomenorrhoea and hirsutism, weight gain, and impaired glucose tolerance.¹ Red flags that warrant early specialist input and weaning off steroid treatment include the development of skin atrophy, striae, telangiectasias, purpura, acne or rosacea, and hair thinning, along with the presence of cushingoid features such as weight gain, moon facies, central obesity, and buffalo hump.

Despite the hypercortisolism, in time patients may develop secondary adrenal insufficiency, owing to long term suppression of the hypothalamic-pituitary-adrenal (HPA) axis, and adrenal atrophy, owing to the lack of endogenous production of adrenocorticotrophic hormone (ACTH). The low baseline cortisol and ACTH are in keeping with insensitivity to feedback from the HPA axis caused by synthetic glucocorticoids (not detectable by routine assays of cortisol) and loss of endogenous ACTH production.

2 What is the most likely cause of this condition?

Short answer

The development of iatrogenic Cushing's syndrome was probably caused by the cumulative systemic absorption of topical, inhaled, and oral steroids.

Long answer

Corticosteroids are a fundamental component of the management of allergic diseases, including atopic eczema,² allergic rhinitis,³ and asthma.⁴ Although oral corticosteroids are most often implicated, inhaled and topical preparations as well as intra-articular and intramuscular injections can also cause adverse effects.

There is no safe dose threshold of treatment with oral steroids because of inter-individual variability in drug absorption and metabolism, so it is difficult to identify patients at risk of HPA axis suppression. However, it is generally accepted that clinical signs of HPA axis suppression may become evident within three months of discontinuing the equivalent of 7.5 mg of prednisolone given daily for longer than three weeks. The systemic effects of inhaled corticosteroids are negligible when doses up to 400 µg/day budesonide equivalent are used, and higher doses or potent preparations like fluticasone are often not necessary, providing little benefit in the control of asthma.⁴ Treatment of skin disease with topical steroid ointments also rarely result in suppression of the HPA axis when used alone, unless highly potent corticosteroids are used or they are applied to an extensive area of the body surface for a long time.⁵⁻⁷ In adults, the HPA axis may also be influenced by drugs that affect steroid metabolism through the cytochrome p450 pathway, including itraconazole and ritonavir.

Limited data are available on the long term effect of corticosteroids on suppression of the HPA axis when combinations of routes are used, and clinicians should be aware of the increased risk of systemic absorption. Further studies are needed to provide good quality recommendations and guidelines.

3 Why did the patient develop fatigue, postural hypotension, and diarrhoea after weaning off treatment?

Short answer

This is indicative of an imminent adrenal crisis.

Long answer

Adrenal crisis is an uncommon but serious consequence of glucocorticoid weaning in patients with suppression of the HPA axis and can be rapidly fatal if left untreated. Acute cortisol deficiency causes blunting of the stress response and a catecholamine resistant state of shock results, with hyponatraemia, hyperkalaemia, hypoglycaemia, and hypercalcaemia.⁸ Owing to the variable and often non-specific clinical signs, diagnosis is often delayed or missed. Clinicians should suspect an adrenal crisis in all steroid dependent patients presenting with hypotension.⁹ In the emergency setting, early parenteral hormone replacement with hydrocortisone and intravenous rehydration with fluids reduces mortality.¹⁰ After improvement, the steroid dosage is tapered to a maintenance level until the HPA axis normalises.

There is no reliable test that predicts the development of an adrenal crisis, but experimental data support the cosyntrophin test (synacthen test) as the primary investigation for secondary

adrenal insufficiency.^{11 12} Monitoring the quality of steroid replacement remains a challenge, owing to a lack of objective methods of assessment, and requires specialist intervention.¹³

To minimise the risk of developing an adrenal crisis, chronic use of glucocorticoids should be gradually reduced rather than abruptly interrupted. Evidence regarding the recovery rate of the adrenal gland is limited, and the efficacy and safety of different withdrawal regimens remain to be established.¹⁴

4 What clinical strategies can be used to minimise systemic absorption of topical steroids in atopic eczema?

Short answer

To minimise the risk of adverse effects we advise keeping the potency of the steroid ointment used, the frequency of applications, the extent of the body surface area treated, and the length of treatment to a minimum.

Long answer

Adverse effects after prolonged use of steroids are most common in children and older people, where absorption is increased because of a high surface to body weight ratio and decreased drug metabolism.^{15 16} Systemic absorption of topical treatment is increased in areas with a thin epidermal barrier and in broken or inflamed skin,¹⁷ particularly in psoriasis.¹⁸

The box outlines the clinical strategies that clinicians should use to minimise the degree of absorption of topical drugs. These should be used in conjunction with frequent follow-up and meticulous clinical examination for signs of suppression of the HPA axis.

Patient outcome

Our patient remained on maintenance steroid replacement therapy with oral hydrocortisone 10 mg daily for many months before ending treatment in 2012. She remains under the care of dermatology for azathioprine treatment, which provides excellent control of her eczema. She continues to use beclomethasone dipropionate inhaler 400 µg twice daily for asthma.

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Clinical strategies to help minimise systemic absorption of topical drugs^{2 19}

Tailor the potency of corticosteroids to the severity of disease

Advise patients to apply topical treatment to the affected area only

Limit use to once daily unless very severe or during an acute flare

Limit the length of treatment—advise patients to use only intermittently for periods of active disease (7-14 days), followed by a “holiday period” using alternative treatments (such as emollients)

Offer practical advice for use and application, including volume to apply (for example, fingertip units)²⁰

Limit the use of repeat prescriptions and regularly review the patient for side effects

Patients should not use potent corticosteroids without dermatology specialist supervision