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lesson of the month (1)

Addison's disease masked by long term exogenous steroid treatment for presumed polymyalgia rheumatica

Addison's disease can present insidiously. A 78-year-old woman presented with non-specific symptoms and hyponatremia, with a previous history of polymyalgia rheumatica treated with glucocorticoids. Subsequent investigations were consistent with primary rather than secondary adrenal failure. Primary autoimmune Addison's disease can present with protean symptoms and diagnosis is often delayed. A high index of suspicion remains the cornerstone of diagnosis.

Corticosteroids are used widely in medicine to treat a variety of disorders. Long-term steroid therapy can result in significant secondary adrenal failure which, if unrecognised during intercurrent illness, can precipitate life-threatening adrenal crisis. It is important to differentiate autoimmune-mediated Addison's disease from secondary adrenal failure as therapy differs with regard to mineralocorticoid replacement and the risks of developing other autoimmune conditions which require long-term surveillance and treatment.

Lesson

A 78-year-old female presented acutely with an 18-month history of non-specific symptoms including lethargy, low mood, poor memory, reduced appetite and weight loss of 6 kg. These symptoms were attributed to depression by her general practitioner and she had been prescribed fluoxetine two weeks prior to this presentation. Her carers described a long history of salt craving in the patient.

The patient had a history of pernicious anaemia and osteoporosis. She was diagnosed with polymyalgia rheumatica in 2001 and was treated with prednisolone 3 mg once daily. Prednisolone was discontinued six months prior to this presentation when the initial diagnosis was revisited.

On initial examination the patient looked lethargic and unwell. Systemic examination was unremarkable. Investigations revealed serum sodium 117 mmol/l and serum potassium 5.5 mmol/l. Full blood count, renal function, liver function and bone chemistry were normal. Spot urine sodium was 119 mmol/l. A diagnosis of hyponatraemia secondary to fluoxetine was made and the drug was discontinued. Forty-eight hours after admission she became progressively unwell and drowsy. On examination she looked dehydrated and generalised hyperpigmentation was noted at this point. She had marked orthostatic hypotension (blood pressure (BP) 130/72 mmHg lying; BP 88/44 mmHg standing). Investigations showed severe hyponatraemia (serum sodium 107 mmol/l). Primary adrenal insufficiency was considered as a diagnosis and treatment with intravenous isotonic saline and hydrocortisone was commenced.

Subsequent short adrenocorticotropic hormone (ACTH) stimulation (Synacthen®) test confirmed adrenal insufficiency (baseline cortisol 119 nmol/l, 30 minutes 326 nmol/l, 60 minutes 243 nmol/l). Adrenal antibodies were positive and abdominal computed tomography (CT) scan showed no evidence of malignancy. The generalised hyperpigmentaion and positive adrenal antibodies were suggestive of primary adrenal insufficiency (Addison's disease) rather than secondary adrenal failure due to long-term prednisolone therapy. Serum ACTH was inappropriately normal (31 ng/l; reference range 0.1–47) for prevailing cortisol levels during the ACTH stimulation test but could be explained by the fact that the sample was drawn while the patient was on intravenous hydrocortisone. Hypoaldosteronism (serum aldosterone <55 pmol/l; normal 100–850) and raised serum renin levels (16.9 nmol/l/hr; range 0.5–3.5) also support the diagnosis of Addison's disease rather than steroid-induced adrenal suppression. Subsequent long ACTH stimulation test showed a suboptimal cortisol increment at 24 hours (135 nmol/l; normal >900 nmol/l) suggesting primary, rather than secondary, adrenal failure.

The patient improved dramatically with rehydration and parenteral steroid therapy. She was subsequently discharged on oral hydrocortisone 20 mg daily in divided doses and fludrocortisone 100 mcg once daily.

Discussion

Primary adrenal insufficiency (Addison's disease) was originally described by Thomas Addison in 1855. His original series described patients with tuberculous infiltration of the adrenal glands.[1] Estimating the prevalence of the disease is difficult due to lack of robust population-based data. Addison's disease is a rare condition with a reported prevalence of about 120 per million but the incidence may be rising.[2] It can present insidiously with protean symptoms and patients often seek medical attention multiple times before a diagnosis is made. Diagnosis is often delayed because of the non-specific features.[3] Prompt diagnosis of Addison's disease is critical to prevent life-threatening adrenal crisis.

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Long-term steroid therapy can result in secondary adrenal insufficiency due to suppression of the hypothalamic-pituitary-adrenal axis. Systemic intercurrent illness can often precipitate adrenal crisis in such patients if steroid therapy is not increased temporarily to tide over the period of metabolic stress.

The aetiology of adrenal insufficiency can be differentiated by checking serum ACTH which is high in Addison's disease and suppressed in secondary adrenal failure due to hypothalamic or pituitary causes. Adrenocortical autoantibodies to 21-hydroxylase are positive in 80% of patient's with Addison's disease.[4]

Our patient had taken prednisolone for seven years and presented with incipient adrenal crisis six months after this was discontinued. Secondary adrenal failure due to long-term adrenal suppression was initially considered as the cause of adrenal failure but the generalised hyperpigmentation and positive adrenal antibodies suggest a diagnosis of autoimmune Addison's disease. Our patient was fortuitously being partially treated for Addison's disease while on prednisolone for presumed polymyalgia rheumatica, but developed overt adrenal insufficiency when this was discontinued. We are aware of at least one other case in which primary adrenocortical failure was masked by exogenous steroid administration.[5] Our patient subsequently developed primary autoimmune hypothyroidism and this, along with the history of pernicious anaemia, supports a common autoimmune aetiology.

The ubiquitous long-term use of oral glucocorticoids to treat a variety of respiratory, rheumatological and haematological disorders carries the risk of causing adrenal insufficiency. Signs and symptoms of adrenal insufficiency in such patients should be anticipated and treated with 'crisis' dose steroid replacement during metabolic stress. Primary autoimmune Addison's disease often presents with non-specific symptoms and diagnosis is often delayed. A high index of suspicion remains the cornerstone of diagnosis.

References

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lesson of the month (2)

Warfarin-induced skin necrosis

Warfarin-induced skin necrosis is a rare but serious complication of treatment with this commonly prescribed drug. This lesson presents the case of a patient with extensive skin necrosis after inappropriately prolonged warfarinisation and delayed recognition. The condition is briefly reviewed to highlight key features and risk factors.

Lesson

A malnourished 82-year-old woman was referred to the emergency department with an extensive, painful rash. This had worsened despite two weeks treatment for herpes zoster. A month prior to admission she had undergone patellar surgery with a brief interruption of warfarin treatment. Warfarinisation had been commenced a year previously for a postoperative pulmonary embolus. Examination revealed extensive tender and malodorous erythematous plaques with a violacious hue. Central necrotic eschars and vesiculobullous changes were evident and there was involvement of the face, breasts, trunk and limbs (Fig 1).

Warfarin-induced skin necrosis (WISN) was suspected necessitating the cessation of warfarin, and administration of vitamin K and low molecular weight heparin. Broad-spectrum antibiotics, enteral feeding and a three-day course of methylprednisolone, as vasculitis could not be excluded, were commenced. Biopsy of involved skin showed vascular thrombi, patchy necrosis and recent haemorrhage consistent with WISN. No evidence of vasculitis was seen. The erythematous plaques progressively became entirely necrotic. Despite prolonged treatment with intravenous antibiotics, the patient died from overwhelming sepsis and multi-organ failure.

Discussion

WISN typically occurs in obese middle-aged women. Lesions have a propensity for areas with increased subcutaneous fat and

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