Missed Diagnosis

Adrenocorticosteroid deficiency: an unusual cause of fever of unknown origin

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Summary: We report the case of a lady with multiple presentations and admissions with fever. The eventual diagnosis was made of adrenocorticosteroid deficiency.

Introduction

Fever is a manifestation of many diseases, including infections, neoplasia, and collagen vascular diseases. Prolonged fever for which a cause has not been found is usually the atypical presentation of a known disease. Diagnosis is often eventually made by re-examining the patient or repeating simple tests. We report a case of corticosteroid deficiency presenting with fever diagnosed by repeat electrolyte testing.

Case report

A 43 year old obese, non-insulin-dependent diabetic, Greek woman presented many times over a 4 month period to her local hospital with fever, nausea, vomiting and feeling generally unwell. On one occasion she was admitted, but discharged without diagnosis. On readmission, 3 weeks later, she was febrile (38°C), pulse 120 beats/minute, blood pressure 100/60 mmHg and clinically dehydrated. Investigations were as follows: sodium 128 mmol/l, potassium 4.2 mmol/l, urea 4.8 mmol/l, creatinine 0.17 mmol/l, glucose 19.6 mmol/l, pH 7.51, base excess +7.3, bicarbonate 31 mmol/l, haemoglobin 15 g/dl, white cell count $7.0 \times 10^9/l$, and ESR 60 mm/hour. Six sets of blood cultures were negative and computed tomographic scan of the abdomen was normal. A diagnosis of viral infection was made. The patient was rehydrated and symptoms improved. The fever was still present on discharge.

One month later the patient was readmitted still complaining of vomiting, nausea, fatigue and fever. On examination she was again febrile (38.5°C) and dehydrated. Weight loss of 20 kg since the initial

presentation was noted. Investigations showed similar results to the previous admission: sodium 132 mmol/l, potassium 3.9 mmol/l, urea 4.0 mmol/l and creatinine 0.10 mmol/l. In view of the low sodium, plasma cortisol levels were assayed (8 a.m. 25 nmol/l (152–552 nmol/l) and 11 p.m. 29 nmol/l (55–276 nmol/l)), and a short synacthen (tetra-cosactrin) test performed (0 minutes, 3 nmol/l; 30 minutes, 41 nmol/l; and 60 minutes, 71 nmol/l).

The patient was started on dexamethasone and fludrocortisone, with resolution of fever and nausea (Figure 1a) and transferred to another hospital for further investigation. On admission the patient was well, afebrile with no evidence of excess pigmentation. Despite the low plasma cortisol levels, it was thought that steroids could be masking another disease process and were therefore stopped. Thirty-six hours later the patient again became unwell and febrile (Figure 1b). Multiple blood cultures were negative. Repeat cortisol assays confirmed the low levels of <100 nmol/l. ACTH levels were inappropriately low (9 a.m. <15 and 11 p.m. <15 ng/l (<65 ng/l)) and the long Synacthen test showed a good response (day 3 pre-Synacthen cortisol 900 nmol/l and 6 hours after Synacthen 1,200 nmol/l). Other investigations included thyroid function (free thyroxine 19 pmol/l (normal 14–34 pmol/l), thyroid-stimulating hormone, 2.7 μ U/ml) with normal response to thyrotrophin-releasing hormone, prolactin (290 mIU/l (normal 65–455 mIU/l)), growth hormone (3 μ U/ml (<10), oestradiol (263 pmol/l (follicular phase μ U/ml 110–1,470 pmol/l) and follicle-stimulating hormone 4 mU/ml (follicular phase 2–8 mU/ml). Antipituitary antibodies and antiadrenal antibodies were negative. Computed tomography and nuclear magnetic resonance scans of the pituitary showed no abnormality.

A diagnosis of isolated ACTH deficiency was made. Fludrocortisone was discontinued and cor-

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Figure 1 (a) Temperature chart after initial steroid treatment. (b) Temperature chart on stopping and restarting steroid treatment.

tisone acetate given in replacement dosage. The patient remains well 6 months later without symptoms on cortisone acetate 12.5 mg twice daily. Interestingly, the diabetes was well controlled on glibenclamide 5 mg twice daily throughout her illness, except during the long Synacthen test when her requirements increased. Since starting maintenance steroids there has been no deterioration of her diabetes control.

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Discussion

This case demonstrates many of the problems in diagnosing both the cause of a fever and corticosteroid deficiency. The diagnosis was made on repeating simple blood tests which, although not typical of corticosteroid deficiency, showed a persistently low sodium. The marked metabolic alkalosis at one of the several presentations could be explained by the persistent vomiting prior to the admission. The lack of hypoglycaemia and failure to show deterioration in plasma glucose control since starting steroids is also atypical.¹

On treatment with corticosteroids the fever in our patient rapidly resolved, returning promptly on stopping steroids and settling with restarting corticosteroids. This supports the fever being due to corticosteroid deficiency, particularly as multiple investigations for other causes of fever including infection and systemic lupus erythematosus were all negative and the patient has remained well. It is reasonable to speculate that the impaired ACTH and corticosteroid production were directly implicated in the production of fever. It is established that interleukin 1, an endogenous pyrogen, stimulates pituitary secretion of ACTH² and that ACTH either directly or through production of corticosteroids suppresses the immune response including interleukin 1 production.³

The diagnosis of cortisol deficiency is often missed and subjects can present over a period of time with symptoms which in retrospect are typical of hypocortisolism. The symptoms of 'pure' glucocorticoid deficiency vary with the acuteness of presentation. Asthenia and hypotension are common symptoms in both acute and chronic deficiency. Anorexia and nausea tend to occur in acute deficiency and weight loss in chronic deficiency. Fever has been reported as a feature of acute glucocorticoid deficiency,^{4–6} but is not listed in most endocrine texts. It is important in any patient that infection and other causes of fever are excluded. Corticosteroids are used in the treatment of many of the causes of fever, but it should be remembered that fever may be a feature of cortisol deficiency itself.