Ectopic ACTH syndrome: redefinition and case report

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Summary
A case is reported which supports the principle that ACTH precursors best characterise so-called ectopic ACTH-syndrome, which should therefore more accurately be referred to as ectopic ACTH-precursor syndrome.

Keywords: ectopic ACTH-precursor syndrome, immunoradiometric assay

In the era of quantification of plasma adrenocorticotrophic hormone (ACTH) by radioimmunoassay, the ectopic ACTH syndrome was perceived to be typically characterised by plasma ACTH levels > 100 ng/l (see box 1),
but this criterion did not take cognisance of the fact that ACTH precursors (better quantified by two-site immunoradiometric assay (IRMA)) constitute the predominant trophic hormone moieties in this entity. The practical application of this principle is exemplified by the patient reported herein.

Case report

This 79-year-old woman presented on 28 November 1994 with a blood pressure of 230/100 mmHg in association with tachypnoea and tender hepatomegaly whilst taking propranolol 10 mg tid and laclidipine 4 mg tid. Her plasma sodium was 125 mmol/l (reference range 135–146), potassium 3.1 mmol/l (3.5–4.8), bicarbonate 22 mmol/l (22–32), chloride 96 mmol/l (101–111), plasma osmolality 259 mOsm/kg by osmometry (285–295) with no corresponding measurement of vasopressin or urinary sodium and osmolality, plasma urea 4.5 mmol/l (2.5–6.5), creatinine 91 μmol/l (40–110), bilirubin 5.9 μmol/l (3–21), alkaline phosphatase 206 IU/l (25–125), γ-glutamyltransferase 312 IU/l (0–45). Chest radiography showed cardiomegaly, pulmonary congestion, and patchy consolidation in the right upper and midzones. No abnormality was detected on hepatic ultrasonography. The plasma potassium subsequently fell to 2.8 mmol/l, and this was corrected by coprescription of triamterene 50 mg/day and frusemide 40 mg/day with consequent increase in plasma potassium to 4.8 mmol/l, although the plasma sodium remained depressed in the range 124–130 mmol/l. By the 20 December the plasma alkaline phosphatase had increased to 699 IU/l, with concurrent γ-glutamyltransferase 2561 IU/l. At this juncture the provisional diagnosis was one of adrenal metastases giving rise to hypotensive hypoadrenalism and metastatic liver disease. The short synacthen test was performed at 09.00 h on 21 December (table), followed that afternoon by an axial computed tomography (CT) scan which showed bilateral adrenal hyperplasia in association with diffuse hepatic metastases (figure). In view of the revised provisional diagnosis of ectopic ACTH precursor syndrome, further blood samples were taken at 16.30 h for plasma ACTH and serum cortisol (table). A chest radiograph taken concurrently

Figure Axial CT scan showing diffuse carcinomatous infiltration of the liver, and bilateral adrenal hyperplasia (arrows)

Biochemical criteria for ectopic ACTH syndrome
- plasma potassium < 3.0 mmol/l
- plasma bicarbonate > 30 mmol/l
- serum cortisol at 09.00 h or midnight > 800 nmol/l
- urinary free cortisol > 1300 nmol/24 h
- plasma ACTH > 100 ng/l
- additional tests: high-dose dexamethasone suppression, response to metyrapone

From

Revised criteria for ectopic ACTH-precursor syndrome
- plasma ACTH precursors > 139 pmol/l
- ACTH precursor/ACTH ratio ≈ 48 or more (precise cut-off level not yet defined)

From

Box 1
showed mediastinal enlargement suggestive of malignant lymphadenopathy. The patient died the following day.

**Comment**

The disproportionate increase in the secretion of ACTH precursors vs ACTH 1-39 shown here proved to be the most decisive validation of the diagnostic criteria for the ectopic ACTH-precursor syndrome (box 1) proposed by Stewart et al. Other insights provided by this case included radiographic documentation of adrenal hyperplasia resulting from trophic hormone hypersecretion, and consequent adrenal hyperreactivity following exogenous ACTH, far in excess of levels recorded in the era when this was a diagnostic test for adrenal hyperplasia. This is a test which could usefully be reintroduced as an adjunct to 24-h urinary free cortisol measurement should two-site IRMA be unavailable or unaffordable in cases of suspected ectopic ACTH-precursor syndrome. In the present instance it was unfortunate that plasma ACTH was measured after exogenous dosing with 250 μg ACTH 1-24, but in the event, the latter preparation does not cross-react with the two-site IRMA (personal communication, John Kane, Principal Biochemist, Hope Hospital, Manchester).

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