A case of ectopic ACTH syndrome: diagnostic difficulties caused by intermittent hormone secretion

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Abstract. A patient with a thymic carcinoid tumour causing ectopic ACTH syndrome is presented. The case illustrates the rapid development of the clinical and laboratory findings often associated with ectopic secretion of ACTH, including severe proximal myopathy, emotional lability, and hypokalaemic alkalosis. Interpretation of conventional tests of pituitary-adrenal function was complicated by intermittent secretion of ACTH by the tumour. The results of selective venous sampling for ACTH ruled out pituitary ACTH hypersecretion and were suggestive of a thymic source; computerized tomography of the chest localized the tumour. In vivo and in vitro investigations confirmed excessive ACTH production by the tumour, and surgical resection plus radiotherapy has resulted in resolution of the syndrome. The diagnostic problems created by intermittent secretion of ACTH by these tumours and the pre-operative and post-operative medical management of these patients are discussed.

Ectopic secretion of ACTH by various non-pituitary tumours was first demonstrated by Meador et al. (1962), long after the initial report by Brown (1928), of a patient with Cushing's syndrome and oat cell carcinoma of the lung. Patients with ectopic ACTH secretion may present either with typical Cushingoid features or with weight loss, proximal myopathy, hypokalaemia, hypertension, and diabetes, but without the typical Cushingoid habitus; the latter group of patients frequently harbour malignant tumours, and their prognosis has been poor (Orth 1981).

In this paper, we describe the presentation, diagnosis, pathologic findings, and successful management of a woman with an occult, malignant, ACTH-secreting thymic carcinoid tumour and discuss some of the problems involved in the localization of such tumours and the diagnostic difficulties resulting from intermittent hormone secretion by these tumours.

Methods

Urinary neutral-17 ketosteroids and the 17-hydroxycorticosteroid excretion, after sodium metaperiodate oxidation, were measured by the Zimmerman reaction. Urine free cortisol was measured using the method of Mattingly et al. (1964). Creatinine excretion was measured simultaneously on each urine specimen to ensure adequacy of the collection. Plasma cortisol was measured by means of radioimmunoassay using the Gamma Coat [125I]cortisol kit (Clinical Assays, Cambridge, MA).

Plasma ACTH radioimmunoassay was performed minor modifications of published methods using antiserum R1543 (Orth 1979). Tumour and normal thymic tissues were frozen immediately after surgical removal, lyophilized, and extracted into 40 and 80 vol of boiling
water, respectively. Aliquots of the extracts were frozen at −70°C and thawed only once for ACTH radioimmunoassay.

Tumour tissue removed at the time of surgery was finely minced under sterile conditions and was distributed in 60 mm culture dishes (Falcon Plastics) in RPMI 1640 medium (GIBCO) supplemented with 20% foetal calf serum (Reheis) with added antibiotics. Spent medium was aspirated and replaced with fresh medium every 3–4 days. Spent medium was centrifuged at 6,000 × g for 15 min, and aliquots of the supernate were frozen at −70°C until assayed.

Immunohistochemical staining for ACTH was performed by Dr. David Page by incubation overnight with rabbit anti-ACTH, directed toward the 11–24 end. The Sternberger PAP technique was utilized, applying a goat anti-rabbit antibody over the anti-ACTH antibody followed by a single step using the soluble rabbit peroxidase anti-peroxidase complexes (Cappell Co.).

Case Report
A 21 year old woman presented to the emergency department with a 1 month history of leg cramps, weakness, easy fatigability, and emotional lability. A 3 months history of amenorrhoea, severe acne, and increasing facial hair growth was also obtained. Because of these symptoms, hypertension (160/104 mmHg), and severe hypokalaemia (2.5 mEq/l), the diagnosis of Cushing’s syndrome was considered. Further outpatient investigations revealed slightly elevated urinary excretion of 17-ketosteroids (17-KS), 17-ketogenic steroids (17-KGS) and free cortisol (Table 1). Early morning plasma cortisol was not suppressed (116 μg/100 ml) after 1 mg of dexamethasone taken at midnight.

She was admitted to hospital. Physical examination revealed an anxious, depressed woman given to inappropriate outbursts of crying. She demonstrated pressure of speech, shortened attention span, and irrational thought processes. Her blood pressure was 160/120 mmHg, her weight was 57 kg, and her height was 173 cm. An acniform rash was present over the face, upper trunk, and arms. She had mild facial hirsutism, oral candidiasis, and a 3 × 1 cm purple stria on the lateral aspect of the left breast. Absence of the following was notable: obesity, rounded facies, enlarged dorsocervical or supraclavicular fat pads, skin fragility, wasting of the extremities, or increased pigmentation. However, she did manifest a severe proximal myopathy affecting the lower more than the upper extremities. A congenitally displaced kidney was easily palpable in the left upper abdomen. Visual fields and the remainder of the physical examination were normal.

Initial laboratory investigations revealed an haematocrit of 42%, white blood cell count of 13,000 with no eosinophils, plasma glucose of 112 mg/100 ml serum sodium of 140 mEq/l, serum potassium of 2.3 mEq/l, serum bicarbonate of 32 mEq/l, and serum creatine phosphokinase of 32 IU/l. Simultaneous urinary excretion of potassium was inappropriately high (40 mEq/24 h). Oral glucose tolerance was abnormal (506 mg/100 ml at 2 h), and 24-h urinary excretion of steroids was now markedly increased (17-KS, 55 mg; 17-KGS, 62 mg; and free cortisol, 3120 μg) (Table 1). Basal morning plasma cortisol was still very high (121 μg/100 ml), and there was no diurnal variation (plasma cortisol at midnight, 96 μg/100 ml). A skull X-ray revealed a normal sella turcica.

<table>
<thead>
<tr>
<th>Day*</th>
<th>Conditions</th>
<th>17-KS (mg/24 h)</th>
<th>17-KGS (mg/24 h)</th>
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<td>49</td>
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<td></td>
<td>Normal range</td>
<td>5−15</td>
<td>5−18</td>
<td>60−350</td>
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* Day of admission designated day.
** Metyrapone administered orally as 750 mg every 6 h for 6 doses.
+ Dexamethasone administered orally as 2 mg every 6 h for 8 consecutive doses.
On the basis of these findings, we felt the aetiology of the hypercortisolism was most likely to be ectopic ACTH syndrome and proceeded to search for the source of ectopic ACTH secretion. A chest X-ray was interpreted as normal, and a computerized tomographic (CT) scan of the abdomen revealed that both adrenal glands were at the upper limits of normal in size, compatible with bilateral adrenal hyperplasia; there was no evidence of a pancreatic, ovarian, intestinal, or hepatic tumour. Phaeochromocytoma was ruled out by normal urinary excretion of catecholamines. The 24-h urinary excretion of 5-hydroxyindole acetic acid was slightly elevated (13.2 mg; normal < 10 mg), but was not diagnostic of a serotonin-secreting carcinoid tumour. Polytomography of the chest suggested a widened anterior mediastinum, although no definite mass was demonstrated. Because of our strong suspicion that the patient had a non-pituitary source of ACTH secretion, she underwent selective venous catheterization on her seventh hospital day, using the Seldinger technique and a transfemoral approach. A series of simultaneous central and peripheral blood samples were collected from multiple sites.

While awaiting the ACTH radioimmunoassay results, we performed a high-dose dexamethasone suppression test (2 mg of dexamethasone every 6 h for 8 doses). Although there was a greater than 50% suppression of urinary 17-KGS and free cortisol excretion during high-dose dexamethasone administration, suggesting that the patient had pituitary ACTH-dependent Cushing's disease (Table 1), the response was decidedly atypical in that the plasma cortisol level continued to fall the day after the last dose from 53 to 12 μg/100 ml (Fig. 1) and the urinary 17-KGS from 107 to 9 mg/24 h. Thus, the aetiology of her Cushing's syndrome remained unclear.

The patient's mental status had progressively worsened during her evaluation, and on the day after completion of the dexamethasone suppression test she became overtly paranoid and withdrawn. Her hypokalaemia persisted despite massive oral and iv potassium supplementation. Therefore, we decided to proceed quickly with the remainder of her diagnostic studies. A metyrapone test (750 mg orally every 4 h for 6 doses) was begun that evening at 18.00 h. There was no rise in 17-KGS excretion (Table 1) or plasma ACTH, but a dramatic rise of plasma cortisol from < 1 to > 150 μg/100 ml was observed during the 60 h after the test was completed (Fig. 1). Because these plasma cortisol results were not immediately available to us, we proceeded to infuse 40 units of ACTH over 12 h and measure plasma and urinary steroids in order to be certain that the previous abrupt and progressive fall in plasma cortisol from 132 to < 1 μg/100 ml (Fig. 1) had not resulted from infarction of the adrenal glands, rather than from administration of dexamethasone and metyrapone. Free cortisol excretion increased from 19,500 to 52,000 μg per 24 h, demonstrating that the adrenal glands were intact.

The results of the venous catheterization study revealed peripheral plasma immunoreactive ACTH levels ranging from 75 to 225 pg/ml; all were inappropriately elevated for the degree of hypercortisolism. The highest central value (280 pg/ml) was detected in the left innominate vein at about the level the thymic vein would be expected to enter; the simultaneous peripheral ACTH was 150 pg/ml, yielding a central-to-peripheral
gradient of 1.7. Although this gradient was not felt to be diagnostic of a mediastinal source of ACTH, it was thought to be suggestive. Review of the lateral view of her initial chest X-ray suggested that the anterior superior mediastinum was more dense than the posterior inferior mediastinum, and a subsequent CT scan of the chest revealed a $6 \times 3 \times 3$ cm anterior mediastinal mass overlying the pulmonary outflow tract (Fig. 2). The patient was felt to have Cushing’s syndrome due to episodic ectopic secretion of ACTH by an anterior mediastinal, probably a thymic, tumour.

She was prepared for surgery with metyrapone, 750 mg orally every 6 h, and 0.25 mg of dexamethasone every 8 h for 1 week. At surgery a 28 g thymic carcinoid tumour adherent to and invading the pericardium was resected along with a pericardial segment. During surgery, blood was obtained simultaneously from an artery supplying and vein draining the tumour: no arteriovenous gradient of ACTH was demonstrated, the arterial plasma ACTH and venous ACTH being 285 and 255 pg/ml, respectively. However, plasma ACTH levels fell promptly following resection of the tumour. The patient made an uneventful post-operative recovery and subsequently received 4000 rads of external irradiation to the mediastinum over 5 weeks.

Immediately post-operatively, she was provided with supplemental steroid therapy which was subsequently tapered to maintenance doses of dexamethasone, 0.25 mg each morning and 0.5 mg upon retiring, so that plasma cortisol and ACTH levels could be followed as tumour markers. As an outpatient her mental dysfunction, hypertension, and acne resolved, her menses and strength returned, and her metabolic aberrations disappeared. Plasma cortisol and ACTH have remained undetectable 24 months post-surgery on maintenance dexamethasone, and repeat CT scan of the chest has shown no evidence of tumour recurrence.

Pathological studies

The tumour was solid, but the cut surface revealed foci of haemorrhage. The tumour had a lobular structure with a very vascular stroma. These neoplastic cells were characterized by central, round to oval vesicular nuclei and ill-defined, acidophilic cytoplasm. The majority of tumour cells showed striking variability of nuclei with numerous mitoses. The most striking feature of the tumour was the presence of multiple foci of lymphatic vessel permeation by tumour cells. Although the tumour grossly was well-circumscribed, the capsule and pericardium was infiltrated by tumour cells, although the surgical margin was uninvolved.

Histochemically, the tumour cells were found to be argentaffin negative (Fontana-Mason stain) and argyro-

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Fig. 2.
A CT scan of the chest revealing a large anterior mediastinal mass overlying the pulmonary outflow tract.
phil positive (Sevier Munger stain), the typical pattern seen in foregut carcinoid tumours (William & Sandler 1963). On electron microscopy neurosecretory granules (100–120 nm in diameter) were present in the cells. Immunohistochemical staining of the cells for ACTH was positive.

Hormonal studies of tumour tissue

The ACTH content of the tumour was 835 ng/g wet weight, whereas the ACTH content of the patient's normal thymic tissue was <3 ng/g wet weight, demonstrating a 300-fold difference in ACTH content. Tissue culture of the tumour cells revealed in vitro ACTH secretion over a 6 week period (225 pg/ml/day at day 13, 90 pg/ml/day at day 27).

Discussion

The ectopic ACTH syndrome results from hypercortisolaemia caused by secretion of ACTH and/or closely related peptides by non-pituitary tumours. The large majority of these cases are associated with oat cell carcinoma of the lung or with tumours of foregut origin, especially bronchial and thymic carcinoids; other tumours have been implicated less frequently (Orth 1981). This patient illustrates some of the difficulties encountered in the assessment of patients with the ectopic ACTH syndrome, including definitively establishing the cause of the hypercortisolism and the location of the tumour.

Tumour localization in patients with the ectopic ACTH syndrome obviously is of utmost importance, but frequently is very difficult. Many patients are inappropriately subjected to bilateral adrenalectomy before an adequate search for their primary ACTH-secreting tumour has been made. The use of whole body venous catheterization with selective sampling for ACTH can prove invaluable in the assessment of these patients and is generally well tolerated (Corrigan et al. 1978; Rees et al. 1977). It is almost always possible to exclude the pituitary as the source of ACTH secretion in difficult cases such as the present one if samples can be obtained from one or both of the petrosal veins, (Corrigan et al. 1978). Localization of ectopic ACTH-secreting tumours in the mediastinum, thyroid, pancreas (via veins communicating with the left adrenal gland), adrenal medullae, and other organs drained by other than the pulmonary and splanchnic venous systems is sometimes possible (Rees et al. 1977). It is essential that a simultaneous peripheral venous ACTH concentration be determined for each central venous ACTH concentration, because ACTH secretion by the normal pituitary gland and by pituitary and non-pituitary neoplasms is episodic (Gallagher et al. 1973; Krieger et al. 1971), and an increased ACTH concentration at a central sampling site may simply reflect a general transitory increase in plasma ACTH following an episode of secretion by a tissue at a site remote from the central catheter tip. It is only with simultaneous paired samples that a gradient can be established and false-positive results be reduced to a minimum.

The CT scan of the chest localized the thymic tumour in this patient when more conventional radiographic procedures, including lateral tomography, failed. Other investigators have also found CT scanning to be useful in delineating the size, location, and extent of thymic tumours (Aita & Wanamaker 1979). Since approximately 10% of ectopic ACTH-secreting tumours is in the thymus (Orth 1981), CT scanning of the chest of these patients should be performed early in the investigations. If a tumour is identified then a limited catheter study could be performed to confirm this as the source of the ACTH.

Most tumours causing ectopic ACTH syndrome are malignant and are non-resectable when discovered, but there have been several reports of sustained remission of ectopic ACTH syndrome after removal of the tumour (Rees et al. 1977; Hirata et al. 1976; Strott et al. 1968; Pimstone et al. 1972). More recently, combined chemotherapy for oat cell carcinoma of the lung has begun to show some promise (Weiss 1978). Unfortunately, however, these patients are often very ill, with high catabolic rates, severe hypokalaemia, and psychotic disturbances, and are poor candidates for either surgery or chemotherapy. These metabolic derangements can usually quickly be controlled with medical therapy – either metyrapone or metyrapone plus aminoglutethimide (Orth & Liddle 1971; Orth 1981) – to permit tumour-directed therapy to be undertaken. In this patient, metyrapone therapy quickly restored normal circulating levels of cortisol and of potassium (which had been impossible to obtain with potassium supplementation alone).
It is often assumed that both pituitary and non-pituitary tumours secrete their hormones at a relatively constant daily rate, even though several dramatic exceptions have been reported (Bailey 1971; Brown et al. 1973; Rees et al. 1977; Hirata et al. 1976, 1979; Chajek & Romanoff 1976). In fact, hormone secretion by tumours is often hectic, if not frankly cyclical. Intermittent secretion of ACTH in the present patient was evident, although our ability to determine whether it was cyclical or merely episodic was limited by the severity of the patient’s illness and the need for early therapy. The absence of an arteriovenous ACTH gradient across the tumour at the time of surgery is further evidence of episodic secretion by the tumour. That the tumour was the source of the ACTH causing the patient’s Cushing’s syndrome is supported by the following evidence: plasma ACTH levels fell to normal immediately following resection of the tumour; the Cushing’s syndrome resolved post-operatively; ACTH was demonstrated in the tumour both by radioimmunoassay and by immunohistochemistry; and the tumour cells were shown to secrete ACTH in vitro.

One possible explanation for the intermittent secretion of ACTH in our patient is episodes of spontaneous haemorrhage into the tumour resulting in variable periods of diminished hormonal output because of damage of the actively secreting cells. We have no direct evidence for this, but areas of focal haemorrhage are typical of these tumours (Wick et al. 1980; Rosai & Higa 1972) and were present in this one. Whatever the cause, intermittent secretion of hormones by tumours may confuse the interpretation of laboratory investigations and result in diagnostic errors (Stroet et al. 1968; Pimstone et al. 1972). For this reason, in patients in whom hormone-secreting tumours are suspected or in whom the results of dynamic tests are atypical or inconsistent with each other, it is important to perform several different tests, some of which may need to be repeated in order to demonstrate reproducible responses.

Thymic tumours are often thought to be rare sources of ectopic ACTH secretion, but there are more than 20 such cases in the literature, and they probably account for about 10% of all cases (Orth 1981; Salyer et al. 1976). In the past these tumours have been described as thymomas or thymic carcinomas, but several authors now believe that every well-documented case has been a primary carcinoid tumour arising in the thymus and that there is no reported case of primary mediastinal neoplasm causing ectopic ACTH syndrome in which the tumour is definitely not a carcinoid (Rosai & Higa 1972; Salyer et al. 1976). Therefore, these tumours should be regarded as thymic carcinoids, distinct from epithelial thymomas. They behave like carcinoid tumours of other organs in that they are usually locally invasive, frequently metastasize, and are often unresectable when discovered (Wick et al. 1980; Salyer et al. 1976). The clinical course is generally protracted, however, and the majority of patients with unresectable tumours survives for several years with palliative treatment (Wick et al. 1980; Rosai & Higa 1972; Salyer et al. 1976).

We plan to use ACTH and plasma cortisol as two more markers in our patient while maintaining her on a physiologic dose of dexamethasone, two-thirds of which is given at bedtime in order to suppress completely ectopic secretion of ACTH by her pituitary gland. A patient with ectopic secretion of ACTH by an oat cell carcinoma has been reported in whom a clinical response to chemotherapy was paralleled by falling ACTH levels and in whom relapse was antedated by elevation of the ACTH levels (Rees et al. 1977). Another patient with ectopic ACTH syndrome due to a thymic tumour had post-operative ACTH levels consistently in the 30 pg/ml range; after radiotherapy plasma ACTH became undetectable (Rees et al. 1977). However, hormones have often proved disappointing as tumour markers; hormone levels do not correlate well with tumour size, a minimal tumour mass is required to produce detectable peripheral hormone levels, and a tumour that previously secreted a hormone may recur without secreting the hormone.

Some thymic carcinoid tumours appear to respond to palliative radiotherapy (Rees et al. 1977; Salyer et al. 1976). For this reason, we elected to employ radiotherapy as an adjunctive measure in this young woman who had locally invasive disease, despite the apparent complete tumour resection. Although we realize the limitations of using biochemical markers for tumour progression, plasma cortisol and ACTH concentration will be measured periodically, and detectable levels will be taken as presumptive evidence of tumour recurrence. We believe this method is more simple, more economical and perhaps more sensitive than performing repeated dexamethasone suppression tests and CT scans of the thorax.
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