

Ectopic ACTH – A brief overview.

K Dhatariya, PE Harris

Abstract

Cushing's syndrome is one of the most challenging topics in endocrinology. Until recently, the differential diagnosis of Cushing's disease from ectopic ACTH production posed particular problems. Misdiagnosis may occur, as exemplified by the accompanying case report. This has now been largely resolved by the technique of inferior petrosal sinus sampling. The localisation and management of tumours ectopically producing ACTH, however, remains a difficult problem. Both anatomical and functional imaging techniques are required for tumour localisation.

Keywords

ACTH, tumours

Case report

A case report of ectopic ACTH-producing carcinoid tumour mis-diagnosed as Nelson's syndrome

A 46-year-old male was admitted under the neurosurgeons for a decompressive laminectomy. An endocrine opinion was sought in view of a previous diagnosis of Nelson's syndrome.

The patient originally presented in the mid-1980s with weight gain, proximal myopathy and increasing lethargy. The diagnosis of Cushing's syndrome was made. An MRI scan of the pituitary was reported as being normal. The patient was initially treated with metyrapone and 12 months later he underwent bilateral adrenalectomy. Following this, he was maintained on standard replacement therapy. He later developed some skin pigmentation and was diagnosed as having Nelson's syndrome. When he was reviewed on the neurosurgical ward he was noted to be slightly pigmented. He said that his skin pigmentation had remained unchanged for a number of years. He was not Cushingoid. Investigations demonstrated a 9 AM

cortisol of < 30 nmol/L. Serum Adrenocorticotrophic hormone (ACTH) was 134 ng/L (normal < 35). MRI scan of the pituitary was normal. Inferior petrosal sinus sampling with CRF failed to demonstrate a gradient, thereby excluding a pituitary source for ACTH¹. Pentetreotide scan demonstrated strongly positive uptake to the left of the mid-line in the thorax. PET scan was also positive at the same location. Both MRI and high resolution CT scans of the chest failed to localise the tumour. Selective venous sampling was likewise unhelpful. Bronchoscopy failed to demonstrate an endobronchial lesion. These data were felt to be consistent with a bronchial carcinoid tumour producing ACTH. The patient underwent surgery and a 2.5 cm carcinoid tumour was resected from the left hilum. The tumour was positively identified at surgery following the preoperative injection of ¹¹¹In-labelled octreotide. Immunocytochemistry confirmed that this was an ACTH producing tumour. Post-operative 9 AM serum ACTH remained elevated at 60 ng/L. Repeat pentetreotide and PET scans confirmed the presence of residual tumour. The patient has now undergone post-operative radiotherapy.

Discussion

The term ectopic was first suggested by Liddle² in the mid 1960's as a term for hormones secreted by tissues other than those normally responsible for their production. Prior to this Brown had reported the first case of ectopic ACTH in 1928 in a patient who had Cushing's syndrome with bilateral adrenal cortical hyperplasia and at post mortem was found

K Dhatariya,

PE Harris*

*Department of
Endocrinology,
King's College Hospital
London SE5 9PJ

Correspondence:

Dr. Ketan Dhatariya,
25, Broomfield Road,
Bexleyheath,
Kent DA6 7PD
UK

Tel: +44 (0) 1322 523231
+44 (0) 1322 522272

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to have a small cell carcinoma of the lung.³ ACTH itself was first isolated and characterised over 50 years ago by Kendall, Hench and Reichstein, for which they won the Nobel Prize in Physiology and Medicine.⁴

In common with other ectopic hormone production, the diagnosis of ectopic ACTH production depends on a number of criteria⁵

1. There is an association of the tumour with an endocrine syndrome
2. Even though the endocrine syndrome may not be clinically apparent there is an elevated or inappropriately raised level of the hormone
3. Removal or suppression of the tumour induces a regression of the endocrinopathy and a reduction in the plasma hormone level
4. The clinical picture is unaffected by removal of the organ that normally secretes the hormone
5. The hormone level is higher in venous blood draining the tumour than in the arterial blood supplying it
6. Extraction or immunocytochemical analysis shows a higher concentration of the hormone in the tumour than in the surrounding non-

• Small cell carcinoma of the lung	(Lung tumors represent up to 50% of cases)
• Bronchial carcinoid	
• Thymic carcinoid ⁷	
• Islet cell pancreatic tumours ⁸	
• Pheochromocytoma ⁹	
• Medullary carcinoma of the thyroid ¹⁰	
• Breast carcinoma ^{*11}	
• Tracheal carcinoma ^{*12}	
• Gastric carcinoma ^{*13}	
• Ileal carcinoma ^{*14}	
• Appendicular carcinoid ^{*15}	
• Colonic carcinoma ^{*16}	
• Ovarian carcinoma ^{*17}	
• Prostatic carcinoma ^{*18}	
• Carcinoma of the cervix ^{*19}	
• Small cell carcinoma of the vagina ^{*20}	
• Paraganglioma ^{*21}	
• Melanoma ^{*22}	
• Others** (include nasopharyngeal carcinoma and salivary gland adenoid cystic carcinoma)	

* - less common, ** - very rare

Table 1. Types of neoplasm associated with ectopic ACTH production

- involved tissue
7. *In vitro*, the tumour cells synthesise specifically identifiable hormone
 8. On mRNA testing of tumour tissue there is evidence that the tumour is producing the hormone

Ectopic ACTH secreting tumours outside of the pituitary are embryologically of neuroectodermal in origin with the ACTH they

produce immunologically identical to the natural α^{1-39} ACTH. Ectopic ACTH production is the most common paraneoplastic hormonal syndrome and it leads to a well-defined clinical picture⁶ with between 10 to 20% of all cases of endogenous Cushing's syndrome being attributable to ectopic ACTH production. There is a 3:1 male to female distribution. It is most often produced from a bronchial carcinoma but may be produced from many neoplastic lesions (see Table 1)

Patients may present with the symptoms of the underlying malignancy and the disease may progress so fast that they may not develop all of the classical signs of Cushing's syndrome as demonstrated by our patient. It is only rarely that Cushing's syndrome is the initial manifestation of the underlying neoplasm but occasionally the ectopic production is a result of a relatively slow growing benign tumour – usually a bronchial carcinoid. Ectopic ACTH is often associated initially with a persistent and profound hypokalaemic alkalosis ($K^+ < 3.2$ mmol/l, $HCO_3^- > 30$ mmol/l) the hypokalaemia due to the mineralocorticoid activity of the cortisol, corticosterone and 11 deoxycorticosterone that may also be present. Occasionally there is an abnormality of the cortisol deactivating enzyme, 11 β hydroxysteroid dehydrogenase aggravating the problem.²³ There is also an associated hyperpigmentation with weight loss, polyuria, polydipsia, muscle weakness and wasting. Hypokalaemia is extremely rare in Cushing's disease and may only be seen in very aggressive cases.

The mechanism of ectopic hormone production has yet to be fully elucidated, but probably involves the 'de-differentiation' of tumour cells with an activation and ultimate expression of the genes that are responsible for pro-opiomelanocortin production. Many non-pituitary cell lines are capable of producing this polypeptide but depending on where the lesion is often dictates what hormone is produced, with bronchial tumours more likely to produce ACTH, islet cell tumours produce insulin, gastrin, vasopressin, glucagon, β HCG, α - or β -MSH, calcitonin or α -feto protein. It is for this reason that these hormones should also be screened for when searching for the site of the tumour.

If Cushing's syndrome is suspected then the course of investigations should include investigations to show the loss of normal circadian rhythm, with inappropriately high midnight cortisol and ACTH levels and an

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	Ectopic ACTH (% of cases)	Cushing's Disease (% of cases)
Hypokalaemia (K+ <3.2 mmol/l)	100†	10
Diabetes mellitus	78	38
Dexamethasone 8 mg/day (no suppression)	89	22
No response to metyrapone	50	36
CRH test excessive response	0	>90

†This is true for small cell carcinoma of the lung, but K⁺ may be normal for bronchial carcinoid.

Table 2. Response to tests used to differentiate ectopic ACTH secretion from Pituitary dependant Cushing's disease

elevated 24 hour urinary free cortisol. Once this has been established, most investigators agree with the use of low and high dose dexamethasone suppression tests (DST). 80% of pituitary adenomas are suppressed by over 50% by the high dose DST. Failure of suppression with the high dose DST in ACTH dependant disease is highly suggestive of ectopic

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ACTH production. A Corticotrophin Releasing Hormone (CRH) test would not usually cause a further elevation of ACTH – unlike the pituitary adenomas, the majority of which will produce an exaggerated response (see table 2). The combination of suppression with a high dose dexamethasone suppression test and an exaggerated CRH response almost always leads to the diagnosis being a pituitary adenoma. A diagnostic dilemma is often encountered if the ACTH is only marginally raised and may be falsely interpreted as a pituitary adenoma. In addition, Cushing's syndrome may be periodic leading to 'cyclical Cushing's syndrome' meaning that if there is a high clinical index of suspicion, negative results may be misleading and so may need to be repeated.²⁴ Alcoholic pseudo-Cushing's²⁵ and depression²⁶ may also lead to diagnostic errors. The insulin stress test may be used to differentiate pseudo-Cushing's from true Cushing's syndrome. Patients with pseudo-Cushing's show a rise in ACTH and

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