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Original article

Ectopic ACTH syndrome: Molecular bases and clinical heterogeneity

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Summary

There are roughly two types of ectopic ACTH syndrome (EAS), one associated with overt malignancies and one with occult neoplasms. The prototype of the first condition is Cushing's syndrome sustained by small-cell lung cancer (SCLC), while bronchial carcinoid tumors are the most common occult sources of ACTH. Patients with EAS and SCLC may have an atypical presentation with muscle wasting and weight loss that are more frequently observed than the classic cushingoid features. These patients have a poor prognosis because SCLC associated with the EAS is more resistant to chemotherapy and the severe hypercortisolism is responsible for a high rate of life-threatening complications during treatment. Conversely, the clinical and biochemical features of the EAS associated with carcinoid may overlap those seen in pituitary-dependent Cushing's syndrome. An extensive radiological and hormonal work-up is necessary to detect the extrapituitary source of ACTH. However, the differentiation between the pituitary, or eutopic, from the non-pituitary, or ectopic, source of ACTH secretion may be extremely difficult in some cases despite the wide diagnostic armamentarium available. Molecular biology studies have demonstrated that the carcinoid cells achieve a process of corticotroph differentiation being able to express the proopiomelanocortin (POMC) gene and to process POMC correctly to release large amounts of intact ACTH. Conversely, SCLC processes POMC in an aberrant way releasing high concentrations of ACTH precursors and less intact ACTH in the circulation.

Key words: ACTH, carcinoid, cortisol, Cushing's syndrome, ectopic secretion, small-cell lung cancer

Background

The definition 'ectopic ACTH syndrome' (EAS) applies to a condition of endogenous hypercortisolism sustained by an ACTH-secreting non-pituitary tumor. The term 'ectopic' means that ACTH is produced and released in an unsuited place and it is in antithesis to the 'eutopic' pituitary origin of ACTH in physiological states or in Cushing's disease (pituitary adenoma). In exceedingly rare cases the non-pituitary tumor secretes the corticotropin releasing hormone (CRH) which eventually stimulates pituitary ACTH release [1]. The EAS accounts for approximately 15% of all cases of endogenous Cushing's syndrome [2], but it may be underestimated (Table I).

Odell et al. [3] have suggested that the term ectopic ACTH syndrome is a misnomer since ACTH, or Proopiomelanocortin (POMC) immunoreactivity and POMC mRNA have been found in virtually all tissues. ACTH is produced via the proteolytic conversion of its inactive precursor, POMC [4]. Then, POMC cleavage by prohormone convertase PC 1/3 in the anterior pituitary gives rise to ACTH and β-lipotropin, along with small amounts of β-endorphin. In physiological conditions, POMC gene is transcripted using the P3 promoter in non-pituitary tissues, thus generating a shorter mRNA that is not translated. Conversely, the non-pituitary ACTH-secreting tumors use the pituitary, P2, promoter or the P1 promoter generating a pituitary size mRNA [5]. Therefore, the EAS is not due to ectopic hormone production but represents a cancer-induced amplification of a biologic feature that normally exists in the cells from which the cancer originates [6].

A large variety of benign and malignant tumors of non-pituitary tissues have been associated with the EAS. These neuroendocrine tumors have been described in virtually every organ of the body. The clinical heterogeneity of the EAS depends mainly on the malignant potential of the underlying tumor, which has a wide spectrum of severity from fast-growing, rapidly progressing cancers, like small-cell lung cancer (SCLC), to slow-growing, indolent carcinoids [7]. In the more recent series, the number of SCLC is progressively decreasing while the number of bronchial carcinoids is increasing as a result of the EAS [2]. This may be the

Table I. Etiology of Cushing's syndrome.

ACTH-dependent Cushing's syndrome	
Cushing's disease	70%
Ectopic Cushing's syndrome	15%
Adrenal Cushing's syndrome	
Adrenal adenoma	10%
Adrenal carcinoma	≅ 5%
Micronodular hyperplasia	≅ 1%
Macronodular hyperplasia	≅ 1%
Iatrogenic Cushing's syndrome	

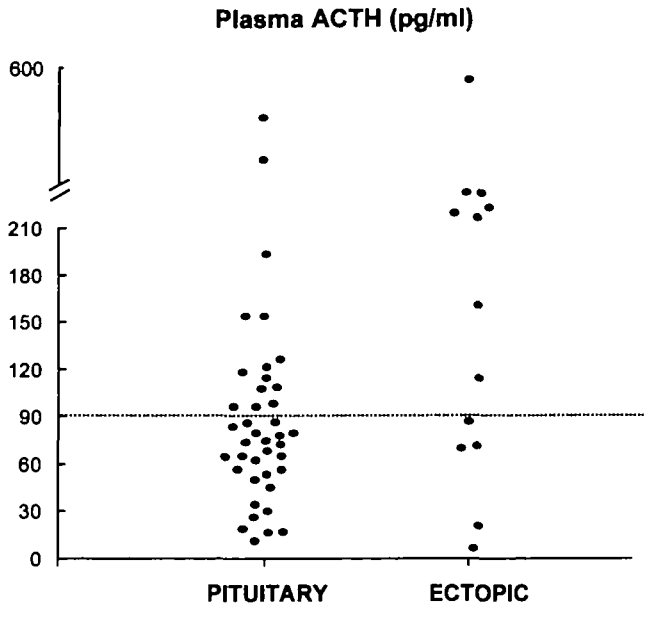

Figure 1. Plasma ACTH concentrations in our series of patients with pituitary or ectopic Cushing's syndrome. The dotted line identifies the upper normal level.

result of a reporting bias due to the greater interest of the endocrinologist for these tumors. However, almost any tumor may attain neuroendocrine differentiation and cause the EAS.

Molecular bases

The tumors causing the EAS, particularly the more malignant ones, show an aberrant processing of the POMC resulting in large underprocessed molecules, like pro-ACTH, or in the activation of abnormal cleavage sites generating fragments, like CLIP or β-MSH, not usually seen in the anterior pituitary [8, 9]. The serum concentrations of the ACTH precursors, like POMC or pro-ACTH, may be extremely elevated in patients with SCLC and the EAS, while the ACTH levels are less markedly elevated [10]. Our experience confirms that a large overlap exists between the ACTH levels observed in ectopic or in pituitary Cushing's syndrome (Figure 1).

Molecular biology helps us to understand the differences between the EAS associated with bronchial carcinoid, as the prototype of indolent tumors, and that of SCLC, as the prototype of aggressive tumors. SCLC expresses the POMC gene that is transcripted by the upstream promoter generating a large-size mRNA and processes POMC in an aberrant way, releasing ACTH precursors of large molecular weight in the circulation. The carcinoid expresses the POMC gene, which is transcripted by the usual promoter generating a normal-size mRNA, and processes POMC normally to release large amounts of intact ACTH [11]. The carcinoid, but not the SCLC, often expresses the vasopressin V3 receptor: a receptor specifically found in the pituitary [12]. V3 receptor gene expression was detected only in ACTH-secreting tumors and not in prolactin- or GH-secreting tumors; therefore, it may be used as a biologic marker of corticotroph phenotype [12, 13]. Therefore, the carcinoid cells may achieve a process of corticotroph differentiation that makes them very similar to the ACTH-secreting pituitary cells [11].

The parallelism between carcinoid and corticotroph cells is made closer by the fact that bronchial carcinoid may express functional glucocorticoid receptors [14]. In general, higher doses of glucocorticoids are needed to suppress POMC gene transcription in the tumor cells than in the pituitary, but in some cases the mechanism may work normally. This may explain how in some patients with the EAS, cortisol is fully suppressed after 8 mg dexamethasone, as it occurs in pituitary Cushing's disease [15].

The outcome of molecular studies has elucidated why an extensive endocrine work-up may also yield pituitary-like responses in a regretfully high number of patients bearing an ACTH-secreting carcinoid. Therefore, it is not surprising that the EAS sustained by carcinoid may be indistinguishable from Cushing's disease on the basis of clinical features and hormonal data [7].

Ectopic ACTH syndrome caused by carcinoid

The differerential diagnosis is challenging because both bronchial carcinoids and pituitary microadenomas are difficult to detect even with sophisticated imaging procedures. The bronchial carcinoid is the ectopic ACTH-producing tumor most likely to elude detection for prolonged periods because of its small size (0.5–1.5 cm) and its usual location in the middle third of the lung, adjacent to pulmonary vasculature from which it cannot be differentiated [16]. The matter is complicated further by the fact that up to 10% of the population in their twenties to forties will have incidental non-secreting tumors of the pituitary gland demonstrable by MRI [17].

As a consequence, many patients with the EAS sustained by bronchial carcinoid are misdiagnosed as having pituitary-dependent Cushing, or undergo bilateral adrenalectomy because the source of ACTH secretion is not found [2]. The term 'occult' EAS has been introduced to define an ACTH-dependent Cushing's syndrome of non-pituitary origin and of more than six months' duration, without the emergence of an obvious source [18]. The gold standard for the differential diagnosis is the contemporary sampling from a peripheral vein and both the inferior petrosal sinuses, the direct effluents of the pituitary, for ACTH measurement. In the event of pituitary Cushing, a center to periphery gradient in ACTH concentrations is found, while in the ectopic Cushing there is no gradient [19] (Figure 2). This is a technically demanding and very expensive procedure that should be performed only by experienced neuroradiologists to avoid misplacement of the catheters or unilateral incannulation of the petrosal sinuses with a following decrease in the diagnostic accuracy [20].

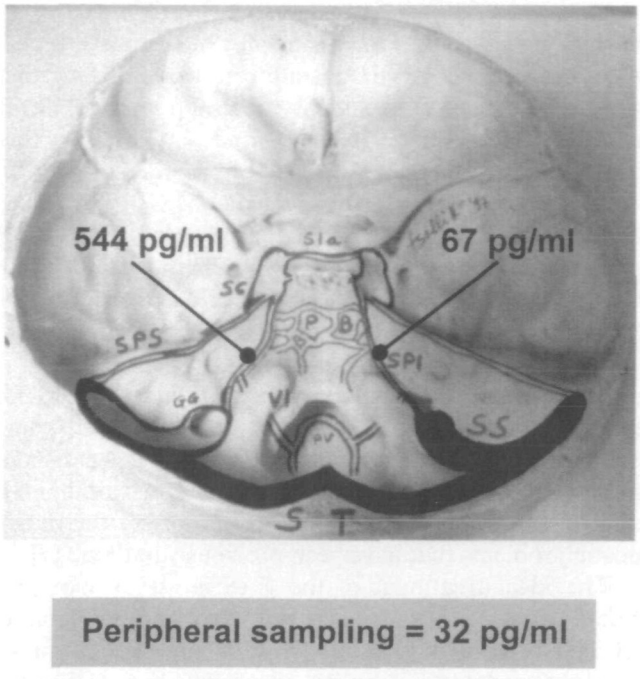

Figure 2. Schematic picture of the vascular anatomy of the pituitary. This is an example of the ACTH concentrations found with simultaneous samplings from the inferior petrosal sinuses and an antecubital vein in one of our patients. The significant ACTH center to periphery gradient is diagnostic for pituitary-dependent Cushing's syndrome.

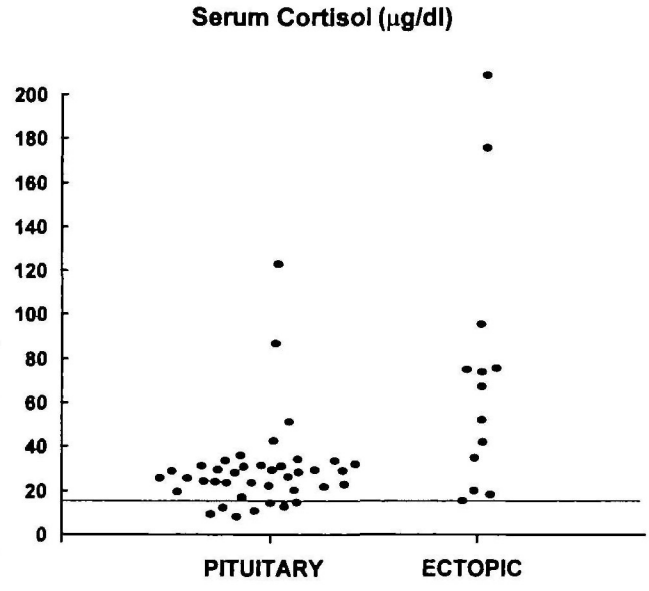

Figure 3. Serum cortisol concentrations in our series of patients with pituitary or ectopic Cushing's syndrome. The dotted line identifies the upper normal level.

From a clinical viewpoint, some elements should be recognized and used in the differentiation between pituitary and non-pituitary ACTH secretion. Hypokalemia with metabolic alkalosis is an important clue because it is much more frequently found in the EAS than in pituitary-dependent Cushing [2]. The clinician may be particularly aware of the EAS in the event of a male patient with cushingoid features, because the female to male ratio is about one in the EAS while it is nine in the pituitary disease. Also, advanced age favors the diagnosis of ectopic Cushing, even if it can occur at any age [2] (Table 2). The complications of hypercortisolism tend to be more severe in the EAS than in pituitary Cushing's disease, in terms of increased blood pressure, hyperglycemia, susceptibility to infections, osteopenia, etc. This is the result of the usually higher cortisol levels observed in ectopic Cushing, albeit with a large overlap with those found in the pituitary disease (Figure 3).

Ectopic ACTH syndrome caused by small-cell lung cancer

The EAS sustained by SCLC, or other aggressive tumors, is a completely different entity. The clinical presentation of Cushing's syndrome is atypical with muscle wasting and weight loss being more frequently observed than the classic signs of hypercortisolism, such as moon facies,

Table 2. San Luigi Hospital series of patients with the ectopic ACTH syndrome (1990–1999).

	Sex	Age	Diagnosis	K^+ (mmol/l)	ACTH (pg/ml)	MRI and/or CT	Octreoscan
1	M	65	SCLC	2.4	691	Positive	–
2	M	55	Neuroblastoma	2.8	100	Positive	Positive
3	F	29	MTC	2.3	150	Positive	–
4	F	26	Bronchial carcinoid	4	205	Positive	Positive
5	M	33	Bronchial carcinoid	2.7	202	Positive	Positive
6	F	34	Pheochromocytoma	2	198	Positive	–
7	F	72	Breast cancer	2.2	110	Positive	–
8	M	71	Pancreatic carcinoid	1.7	170	Positive	Negative
9	M	67	Prostate cancer	3.7	250	Positive	Positive
10	F	28	Occult	3.9	35	Negative	Negative
11	M	62	Bronchial carcinoid	1.8	140	Negative	Positive
12	M	63	SCLC	2.2	250	Positive	Positive
13	F	76	SCLC	2.0	18	Positive	–
14	F	66	SCLC	2.1	160	Positive	–

SCLC – small-cell lung cancer; MTC – medullary thyroid carcinoma.

Table 3. Possible hormonal co-secretion associated with the ectopic ACTH syndrome by different tumor types.

Tumor type	Hormone product	Clinical syndrome
Lung cancer	ADH	SIADH
	PTH	Hypercalcemia
GEP Tumor	Gastrin	Zollinger Ellison's syndrome
	Glucagon	Necrolytic migratory erythema, diabetes mellitus
	VIP	Verner-Morrison's syndrome
Pheochromocytoma	Cathecolamines	Paroxysmal hypertension

truncal obesity, red striae, etc. [21]. A high degree of clinical suspicion is necessary to correctly address signs that may be simply referred to the wasting cancer syndrome.

It is possible to identify immunoreactive ACTH in almost all SCLC tissue extracts, yet only 1% to 5% of SCLCs is associated with Cushing's syndrome [21]. SCLCs associated with the EAS may be inherently more resistant to chemotherapy than other SCLC tumors [22]. Plasma ACTH levels do not correlate directly with tumor burden even if the EAS might be associated with more extensive disease and a worse prognosis [23]. Patients with the EAS at initial presentation of their SCLC had a significantly shorter survival (median survival of about four months) than those with the EAS diagnosed later during the course of their SCLC (median survival of about 11 months) [21–23].

The biologic characteristics of the SCLC causing the EAS do not account fully for the poor prognosis of such patients, and some clinical features are key to the patients' outcome. These patients have a much higher rate of life-threatening complications during chemotherapy, mostly related to severe infections and gastrointestinal bleeding or ulceration [21–24]. The severe and uncontrolled hypercortisolism is directly responsible for these detrimental effects. Additional factors contributing to the bacterial or fungal infections are coexisting diabetes mellitus and metastatic involvement of bone marrow, which seems more frequent in the patients with SCLC and paraneoplastic syndromes [21–24]. As a consequence, up to 82% of patients with SCLC and the EAS died within two weeks from the start of chemotherapy in a recent series of the M.D. Anderson Cancer Center [24]. It may be anticipated that achieving control of cortisol secretion before administering chemotherapy may ameliorate the prognosis of these patients. The use of high doses of inhibitors of steroid biosynthesis should be considered as the first line of treatment given a few weeks before chemotherapy, even if there is the potential for liver toxicity with ketoconazole, the most rapidly effective drug [25].

The clinical heterogeneity of the EAS does not only depend on the biologic behavior of the responsible neoplasm and additional factors can add variability to the clinical presentation. One factor may be the possible co-secretion of other hormones along with ACTH by the tumor. The resulting clinical presentation may be a mixture of Cushingoid features and signs due to the biologic effects of the co-secreted hormones (Table 3). Another factor is that the clinical onset of the EAS could not coincide with that of the responsible neoplasm. The discrepancy is usually characterized by a later appearance of the EAS, often in association with tumor relapse or progression; sometimes, the EAS may precede the discovery of a malignancy. Furthermore, a phenomenon increasingly appreciated in the EAS is intermittent hypercortisolism with long periods of spontaneous remission. The cyclical Cushing's syndrome may be associated with indolent tumors (carcinoids) and this particular secretory pattern adds to the diagnostic problems that have been previously outlined [7].

The ideal treatment of the EAS is removal of the ectopic source of ACTH. However, the malignant ACTH-secreting tumors are usually unresectable and also anti-neoplastic therapy has been employed with limited success. Bilateral adrenalectomy represents an effective palliative measure in patients whose projected life expectancy justifies such a major procedure. Experience with medical therapy in the EAS is relatively limited; mixed results have been reported with adrenal steroid biosynthesis inhibitors (ketoconazole, aminoglutetimide, mitotane), inhibitors of ACTH secretion (octreotide, lanreotide), or glucocorticoid receptor antagonist RU-486 [2]. When the source of ectopic ACTH production has not been detected (occult EAS), medical or surgical therapy is instituted and periodic screening with CT and MRI of the chest and abdomen is necessary [18].

Conclusions

A wide spectrum of clinical and biochemical presentations characterizes the EAS. At one extreme there is the 'classic' ectopic ACTH-producing cancer, whose prototype is the SCLC. The syndrome is rapidly progressive and is characterized by severe clinical manifestations and poor prognosis. When coping with a patient with the EAS sustained by SCLC, the problem is to suspect the atypical presentation of Cushing's syndrome. Once the EAS is suspected, the biochemical confirmation is straightforward because gross elevations in urinary or serum cortisol and plasma ACTH are readily apparent. The tumor is obvious and an extensive endocrine work-up is unnecessary. The major challenge is the therapeutic management of such patients.

At the other extreme of the spectrum is the 'occult' ectopic ACTH-producing tumor, whose prototype is the bronchial carcinoid. The clinical features and hormone data may overlap those seen in pituitary-dependent Cushing's disease. When coping with a patient with the EAS sustained by bronchial carcinoid, the problem is to

obtain biochemical and radiological confirmation of the extra-pituitary source of ACTH secretion. An extensive work-up is often necessary since a single endocrine test cannot lead to the differential diagnosis and many sophisticated imaging procedures are warranted in searching for the tumor. Notwithstanding the many diagnostic efforts, the cause of the EAS may remain unproven for many years or lifelong.

Molecular biology studies have started to clarify some pathophysiological aspects of this intriguing syndrome, and we hope that these will be exploited for the clinical management of these patients in the near future.

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