The Ectopic Adrenocorticotropic Hormone Syndrome

Rarely Easy, Always Challenging

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KEYWORDS

• Ectopic • Cushing's • ACTH • Carcinoid • Neuroendocrine tumor
• Small cell lung cancer

KEY POINTS

- Historically, patients with the ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) presented with aggressive tumors, such as small cell lung cancer, and the abrupt onset of symptoms and signs of severe hypercortisolism; however, the pulmonary carcinoid tumor is now recognized as the most frequent cause of the EAS.
- ACTH-secreting pulmonary carcinoids, like the corticotroph tumors causing Cushing's disease, are often small and difficult to detect; patients typically present with a gradual onset of the classical signs and symptoms of Cushing's syndrome, usually indistinguishable from the presentation of Cushing's disease.
- Differentiating the EAS from Cushing's disease therefore remains challenging and requires a combination of clinical assessment, dynamic biochemical tests, inferior petrosal sinus sampling, and multimodal imaging, each with their own caveats and pitfalls.
- All testing procedures should be considered to be probabilistic rather than algorithmic.

INTRODUCTION

The ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) comprises around 10% to 20% of ACTH-dependent Cushing's syndrome and 5% to 10% of all types of Cushing's syndrome.[1,2] In the past, most EAS patients presented with small cell lung cancer (SCLC).[3,4] However, because of improved imaging techniques and changing referral patterns, over the past 50 years, the spectrum of malignancies associated with the EAS has broadened to include other neuroendocrine tumors (NETs), predominantly pulmonary, thymic, and pancreatic carcinoids, and more rarely, medullary

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thyroid carcinoma (MTC) and pheochromocytoma.[1,2,5] However, virtually any tumor may develop neuroendocrine differentiation and cause the EAS.

The EAS causes significant comorbidity in a patient with a background malignancy. Furthermore, untreated hypercortisolism contributes to excess mortality. In patients with nonmalignant causes of Cushing's syndrome, mortality is increased with a standard mortality ratio between 2.0 and 4.0 with cardiovascular deaths most common.[6,7] Hence, the EAS should be managed aggressively with every effort to establish rapid eucortisolemia and identify the tumor source, which may frequently be amenable to curative surgery.

PREVALENCE OF ECTOPIC ADRENOCORTICOTROPIC HORMONE SYNDROME

The EAS is rare. Studies show the prevalence of EAS is approximately 1% to 5% in patients with SCLC,[8,9] 3% in patients with thoracic or gastroenteropancreatic carcinoids (excluding MEN1),[10] and 0.7% in patients with MTC,[11] although the prevalence may be higher in patients with thymic carcinoids.[12]

MOLECULAR PATHOPHYSIOLOGY

The EAS is caused by abnormal expression of the pro-opiomelanocortin (*POMC*) gene product arising from non–pituitary tumors in response to ectopic activation of the pituitary-specific promoter of this gene.[13] This promoter is embedded within a defined CpG island and, in contrast to somatically expressed CpG island promoters, is methylated in nonexpressing tissues but specifically unmethylated in expressing tissues.[14] POMC promoter activity and its methylation status have been studied in ACTH-secreting thymic carcinoids, with an association demonstrated between hypomethylation of the POMC promoter region and POMC overexpression.[13]

Genetic mutations associated with the EAS are largely unknown. ACTH-secreting carcinoid tumors may harbor germline *MENIN* mutations,[6] and ACTH-secreting MTC or pheochromocytoma may be associated with germline *RET* mutations, although they are much more frequently sporadic.[1,2]

CLINICAL AND BIOCHEMICAL PRESENTATION OF THE ECTOPIC ADRENOCORTICOTROPIC HORMONE SYNDROME

There are epidemiological and clinical features that can help discriminate between the EAS and Cushing's disease (**Table 1**). The age of onset is normally higher in EAS compared with Cushing's disease,[1,15,16] and the gender ratio also differs, with EAS occurring only slightly more often in women compared with the marked female predominance in Cushing's disease.[1,2,6]

In terms of the clinical features of EAS, there is significant heterogeneity related to the malignant potential of the underlying tumor and the severity of the hypercortisolism. SCLCs and other aggressive tumors are usually associated with much higher ACTH and cortisol levels compared with Cushing's disease and subsequently present with rapid onset of clinical signs and symptoms, including hyperpigmentation, weight loss, and mineralocorticoid effects, as opposed to the classical Cushing's syndrome phenotype.[1,2] Moreover, the detection of EAS in a patient with rapidly progressing SCLC with significant catabolic features can sometimes go unnoticed, contributing to significant comorbidity.[5] In contrast, patients with ACTH-secreting carcinoid tumors more often have a gradual onset of the broad classical signs and symptoms of Cushing's syndrome, indistinguishable from the presentation of Cushing's disease.[1,2]