Ectopic Cushing and Other Paraneoplastic Syndromes in Thoracic Neuroendocrine Tumors

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KEYWORDS

• Cushing • Corticotropin • Cortisol • Neuroendocrine tumors • Paraneoplastic syndrome

KEY POINTS

- Overproduction of corticotropin by the pituitary gland or extrapituitary tumors leads to hypercortisolism or Cushing syndrome.
- Diagnosis of suspected Cushing syndrome involves 3 major steps: confirmation of hypercortisolism, differentiation between corticotropin-independent and corticotropin dependent causes of Cushing syndrome, and distinction between pituitary and ectopic corticotropin production.
- When ectopic corticotropin is produced by malignancies, circulating corticotropin and cortisol levels are extremely high, the duration of symptoms is shorter, and the clinical phenotype is atypical compared with pituitary-dependent Cushing disease.
- A definitive diagnosis of ectopic corticotropin secretion should require stringent criteria, including reversal of the clinical picture after resection of the tumor and/or demonstration of corticotropin immunohistochemical staining within the tumor tissue.
- Various neoplasms can produce corticotropin, especially those originating from neuroendocrine cells.
- After small cell lung carcinoma (SCLC) and carcinoid tumors, the subsequent most commonly reported tumors causing ectopic corticotropin secretion are harbored in the thymus (11%) and pancreas (8%).
- The main conclusion that can be drawn from the most recently published series is that more than half of the tumors producing ectopic corticotropin secretion were found in the lung or in the thymus, whereas, including MTC and pheocromocytomas, two-thirds were in the thorax, neck, or adrenal glands.
- As in Cushing disease, major symptoms and signs include central obesity, primary or secondary amenorrhea in female patients, hirsutism, acne, violaceous skin striae, easy bruising, hypertension, glucose metabolism imbalance, fatigue, muscle weakness, mental changes or emotional disturbances, hyperpigmentation, and acanthosis nigricans.
- Due to the difficulties in differentiating the source of ectopic corticotropin and although the ectopic tumor represents the minority of all cases of Cushing syndrome, an accurate biochemical as well as radiological work-up is strongly recommended.

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- Surgery represents first-line treatment in these patients; however, differently from pituitary corticotropin-dependent Cushing, these cases are generally responsive to somatostatin analog therapy, at least in terms of clinical and biochemical control of the paraneoplastic syndrome.
- Hyponatremia is a common feature in patients with lung cancer.
- Ectopic acromegaly is rare, and since the discovery of growth hormone (GH)–releasing hormone (GHRH) approximately 30 years ago, only 74 cases have been reported in the literature.
- Carcinoid syndrome is a rare feature in bronchial carcinoid patients.
- Another rare cause of endocrine syndrome associated with carcinoid tumor is malignant hypercalcemia and includes ectopic production of parathormone (PTH) or PTH-related peptide (PTH-rp) by the tumor.

ECTOPIC CUSHING SYNDROME

Overproduction of corticotropin by the pituitary gland or extrapituitary tumors leads to hypercortisolism or Cushing syndrome.[1,2] Definition and recognition of the 2 forms of corticotropin-dependent Cushing syndrome is a challenging task. Although a majority of these cases are diagnosed as Cushing disease secondary to an corticotropin-secreting pituitary adenoma, 10% to 15% of them may result in the ectopic corticotropin and/or corticotropin-releasing hormone (CRH) overproduction, which is mainly caused by lung or, more rarely, gastroenteropancreatic or other neuroendocrine tumors.[1,3] Cushing syndrome is associated with major morbidity, especially metabolic and cardiovascular complications, osteoporosis, psychiatric changes, and cognitive impairment. Moreover, exacerbation of prior autoimmune diseases is also seen and all of these systemic complications lead to quality-of-life impairment and increased mortality, regardless of the oncologic outcome of the affected patients.

A diagnosis of suspected Cushing syndrome involves 3 major steps: confirmation of hypercortisolism, differentiation between corticotropin independent and corticotropin-dependent causes of Cushing syndrome, and distinction between pituitary and ectopic corticotropin production.[4] Because normalization of cortisol hypersecretion by the selective removal of a pituitary adenoma or of a solitary bronchial carcinoid tumor has a high probability of resolving the condition, it is essential to distinguish ectopic corticotropin secretion from the more common Cushing disease and, in the former, to make every effort to localize the source of ectopic corticotropin production.[4]

Various benign and malignant tumors have been found associated with ectopic corticotropin secretion. In most cases, when ectopic corticotropin is produced by malignancies, circulating corticotropin and cortisol levels are extremely high, the duration of symptoms is shorter, and the clinical phenotype is atypical compared with pituitary-dependent Cushing disease. Conversely, ectopic corticotropin secretion is often associated with several neuroendocrine tumors with different aggressiveness and which produce the typical signs and symptoms of Cushing syndrome, with a biochemical resemblance to pituitary Cushing disease.[4]

For this reason, it has been stated that a definitive diagnosis of ectopic corticotropin secretion should require stringent criteria, including reversal of the clinical picture after resection of the tumor and/or demonstration of corticotropin immunohistochemical staining within the tumor tissue. Unfortunately, however, these criteria are not applicable to several of the reported cases of ectopic corticotropin secretion.[4] Primary lesion resection cannot be curative in disseminated tumors nor can lack of immunostaining in a biopsy specimen disprove ectopic corticotropin secretion, because only a subpopulation of tumor cells within the tumor mass may actually secrete corticotropin.

Various neoplasms can produce corticotropin, especially those originating from neuroendocrine cells. Initially, these tumors have been recognized based on the characteristics of the neoplastic cells, APUD cells.[4] Small cell lung carcinoma (SCLC); carcinoid tumors, especially of the lungs, thymus, and gastrointestinal tract; islet cell cancers; pheochromocytomas; and medullary thyroid carcinomas (MTCs) are the most frequent along with several miscellaneous tumors, including paraganglioma, neuroblastoma, prostate, breast, kidney, stomach, ovary, melanoma, colon, leukemia, and anorectal cancer, which all have been associated with ectopic Cushing syndrome.[4] In the past, SCLCs accounted for most cases of ectopic corticotropin secretion.[4] In recent surveys, however, the preponderance of these tumors has