J Prev Epidemiol. 2026:e39326 Review

doi 10.34172/jpe.39326 Journal of Preventive Epidemiology http jprevepi.com

Paraneoplastic hypercortisolism; mechanisms and management of lung cancer–induced ectopic Cushing syndrome

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Received: 13 Dec. 2025
Revised: 3 Mar. 2026
Accepted: 14 May 2026
ePublished: 25 May 2026

Keywords: Ectopic Cushing syndrome, Small cell lung cancer, Hypercortisolism, Neuroendocrine tumors

Citation: Bitaraf M, Memarian M. Paraneoplastic hypercortisolism; mechanisms and management of lung cancer–induced ectopic Cushing syndrome. J Prev Epidemiol. 2026;x(x):e39326. doi: 10.34172/jpe.39326.

Abstract

Paraneoplastic hypercortisolism from lung cancer-induced ectopic Cushing syndrome (ECS) is a critical condition caused by unregulated secretion of adrenocorticotropic hormone (ACTH) from neuroendocrine lung tumors, notably small cell lung cancer (SCLC). SCLC accounts for most ECS cases, due to its aggressive nature, rapid growth, early metastasis, and strong link to tobacco use. Neuroendocrine lung tumors vary from low-grade carcinoids to highly malignant SCLC and large cell neuroendocrine carcinoma, all capable of ectopic ACTH production that stimulates excess cortisol secretion, causing bilateral adrenal hyperplasia. Ectopic Cushing syndrome manifests with rapidly developing severe symptoms such as hypokalemia, metabolic alkalosis, hypertension, hyperglycemia, muscle weakness, facial puffiness, bruising, and hyperpigmentation. Hypokalemia is particularly dangerous. Diagnosis relies on biochemical evidence of elevated ACTH and cortisol with loss of normal cortisol rhythm, complemented by dynamic tests like dexamethasone suppression, though responses can be atypical. Imaging supports tumor localization, with inferior petrosal sinus sampling considered the gold standard to distinguish ectopic ACTH sources. Management involves controlling cortisol excess using steroidogenesis inhibitors and potassium-sparing diuretics, with bilateral adrenalectomy reserved for refractory cases. Simultaneously, treatment targets the underlying malignancy, mainly with chemotherapy (cisplatin/etoposide), radiation, and sometimes surgery in early stages. Despite treatment advances, prognosis remains poor; median survival for extensive SCLC is under 14 months.

Introduction

Paraneoplastic hypercortisolism, commonly referred to as ectopic Cushing syndrome (ECS), represents a rare but profoundly severe endocrine disorder stemming from the autonomous secretion of adrenocorticotropic hormone (ACTH) by non-pituitary tumors (1). This condition, which leads to excessive cortisol production by the adrenal glands, is particularly associated with lung cancers, notably small cell lung carcinoma (SCLC), and also with bronchial carcinoid tumors and, less frequently, other histological subtypes like large-cell neuroendocrine carcinoma and adenocarcinoma (2,3). Ectopic Cushing syndrome accounts for approximately of all endogenous Cushing syndrome cases, with lung tumors being the predominant source of ectopic ACTH secretion (4). The prevalence of ECS in SCLC patients ranges from 1.6% to 6% (5), though some recent data suggest it may be as high as 18% in specialized centers, often due to under-diagnosis and atypical clinical presentations (6). Multidisciplinary management is crucial for these patients, requiring a coordinated approach involving endocrinologists, oncologists, surgeons, radiologists, and supportive care specialists (7,8). Lung cancer-induced ECS typically presents with a rapid onset and aggressive course, often diverging significantly from the more gradual presentation of pituitary-dependent Cushing disease (6,9). Patients frequently lack the classic cushingoid features like moon facies, truncal obesity, and purple striae, or these signs develop very quickly and are less prominent than severe metabolic derangements (4,10,11). The most striking clinical indicators include severe and often refractory hypokalemia, metabolic alkalosis, resistant hypertension, and new-onset or worsening hyperglycemia (12,13). Proximal muscle weakness, peripheral edema, and fatigue are also commonly observed (14,15). These electrolyte disturbances and myopathy are often more severe in ECS compared to pituitary-dependent forms, a crucial differentiating factor (16,17). Weight

loss is often more prevalent than weight gain in SCLC-associated ECS, contrasting with typical Cushing's disease (4). Meanwhile, biochemically, ECS is characterized by markedly elevated plasma ACTH and cortisol levels, often several times above the upper limit of normal (6,18). The normal diurnal rhythm of cortisol secretion is disrupted (19). Diagnostic tests such as the 24-hour urinary free cortisol frequently show levels dramatically increased, and early morning serum or salivary cortisol measurements are also significantly elevated (20). Dynamic endocrine tests, such as the high-dose dexamethasone suppression test, typically fail to suppress cortisol production (less than 50% suppression), which contrasts with the suppression often seen in pituitary-dependent Cushing disease (21). Similarly, corticotropin-releasing hormone stimulation tests often elicit a blunted or absent ACTH and cortisol response in ectopic cases, supporting a non-pituitary source (22,23). The combination of these biochemical markers and dynamic test results is crucial for suspecting ECS (24). This overview of paraneoplastic hypercortisolism elucidates the key mechanisms and current clinical management strategies for lung cancer-induced ECS, highlighting the critical need for vigilance to diagnose this rare but life-threatening syndrome promptly and to initiate coordinated multidisciplinary treatment.

Key point

Paraneoplastic hypercortisolism due to lung cancer–induced ectopic Cushing syndrome (ECS) is a complex and often life-threatening condition that demands prompt recognition and coordinated management. The pathophysiology centers on unregulated adrenocorticotropic hormone (ACTH) secretion by neuroendocrine lung tumors, leading to severe and rapidly progressive hypercortisolism. Clinical features are often more severe and atypical compared to classic Cushing syndrome, with prominent metabolic and electrolyte disturbances. Diagnosis hinges on biochemical confirmation of hypercortisolism and elevated ACTH, supported by imaging to localize the tumor. Management is twofold: controlling cortisol excess through medical or surgical means and treating the underlying malignancy with chemotherapy, immunotherapy, or targeted agents. While prognosis remains guarded, especially in small cell lung carcinoma, early and aggressive intervention can mitigate complications, improve tolerance of cancer therapy, and enhance both survival and quality of life. Continued advances in endocrine oncology, molecular diagnostics, and targeted therapeutics hold promise for improving outcomes in this challenging syndrome.

Search strategy

For this narrative review, we conducted a literature search across multiple databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase, using a variety of relevant keywords like; ectopic Cushing syndrome, small cell lung cancer, hypercortisolism and neuroendocrine tumors

Mechanisms of lung cancer-induced ectopic ACTH production

The principal pathophysiology of lung cancer-induced ectopic ACTH secretion consists the aberrant expression and processing of the pro-opiomelanocortin (POMC) gene within tumor cells (25,26). The POMC gene normally encodes a precursor protein that is cleaved to produce ACTH and other peptides (27). In ectopic ACTH-producing tumors, particularly SCLC and bronchial carcinoids, there is inappropriate activation of the POMC gene promoter, leading to its transcription outside of the pituitary gland (25,28,29). This aberrant transcription can be driven by epigenetic alterations, specifically the hypomethylation of CpG islands within the POMC promoter region (29,30). This hypomethylation de-represses the promoter, allowing transcription factors like E2F1 to bind and initiate POMC gene expression, a mechanism distinct from the pituitary-specific Tpit/Pitx1 activation (30). This results in the production of biologically active ACTH and often larger, variably bioactive ACTH precursors, which known as big ACTH due to incomplete or aberrant post-translational processing by prohormone convertases (31-33). Neuroendocrine differentiation is a hallmark of many lung tumors associated with ECS, including SCLC, bronchial carcinoids, and large-cell neuroendocrine carcinoma, which possess the cellular machinery for hormone biosynthesis and secretion, such as dense-core secretory granules (34,35). Some ectopic ACTH-secreting tumors may also produce corticotropin-releasing hormone, which can further stimulate tumor ACTH secretion in an autocrine or paracrine loop, exacerbating the hypercortisolemic state (36). Furthermore, dysregulation of the glucocorticoid receptor pathway within tumor cells, including expression of aberrant receptor isoforms or mutations causing glucocorticoid resistance, can diminish the normal negative feedback suppression of POMC and ACTH synthesis, thereby perpetuating the excessive hormone production (37). The rapid onset and severe nature of hypercortisolism in lung cancer-induced ECS is a direct consequence of the aggressive tumor biology and the uncontrolled ectopic hormone production (6, 38).

Diagnosis of ectopic Cushing syndrome

Diagnosis of ECS in the context of lung cancer requires a high index of suspicion, especially in patients with known or suspected malignancy who develop rapid-onset features of hypercortisolism (4,39). Initial biochemical evaluation includes measurement of 24-hour urinary free cortisol, late-night salivary cortisol, or serum cortisol after a low-dose dexamethasone suppression test (20). In ECS, the 24-hour urinary free cortisol levels are typically markedly elevated, and there is no suppression of cortisol with low-dose dexamethasone (4). High-dose dexamethasone suppression testing can help differentiate pituitary from ectopic sources (24); since, in Cushing disease, high-dose dexamethasone often suppresses cortisol by more than 50%, whereas in ECS, suppression is minimal or absent (4,40). Plasma ACTH levels are crucial; meanwhile its high

levels strongly suggest an ectopic source, although overlap exists (41). In some cases, ACTH levels may be only moderately elevated, necessitating further investigation (25,42,43). Additional supportive findings include hypokalemia, metabolic alkalosis, and elevated serum glucose (44). Imaging plays a dual role: identifying the source of ACTH production and staging the underlying malignancy (45,46). Chest computed tomography (CT) is the initial imaging modality of choice, often revealing a lung mass (47). If the primary tumor is not evident, somatostatin receptor imaging like Gallium-68 DOTATATE PET/CT may be useful, particularly for detecting bronchial carcinoids, which frequently express somatostatin receptors (48). In addition, FDG-PET may be more sensitive for SCLC, which tends to be more metabolically active (49). Inferior petrosal sinus sampling, the gold standard for distinguishing pituitary from ectopic ACTH secretion, is generally not required if a clear ectopic source is identified on imaging and ACTH levels are markedly elevated, but it may be considered in diagnostically ambiguous cases (50,51).

Management of lung cancer–induced ECS

The management of lung cancer–induced ECS is challenging and must be individualized based on tumor type, stage, resectability, and the severity of hypercortisolism (52). The overarching goals are to control cortisol excess to prevent life-threatening complications and to treat the underlying malignancy (6). In cases where the tumor is localized and surgically resectable, most commonly bronchial carcinoids complete surgical excision is the treatment of choice and can lead to rapid resolution of hypercortisolism (53,54). Following successful resection, patients require glucocorticoid replacement therapy during the recovery period of the suppressed HPA axis, which may take several months (19). However, in the majority of cases, particularly those involving SCLC, the tumor is metastatic or unresectable at diagnosis, necessitating systemic therapy and medical management of hypercortisolism (6,55). Medical therapy for cortisol excess in ECS aims to inhibit adrenal steroidogenesis, block glucocorticoid receptors, or reduce ACTH production (56). Ketoconazole, an imidazole antifungal agent, was historically a first-line agent due to its ability to inhibit multiple enzymes in the cortisol synthesis pathway, including 11β-hydroxylase and 17α-hydroxylase (57). However, concerns about hepatotoxicity and drug interactions have led to its declining use (58,59). Metyrapone, which inhibits 11β-hydroxylase, is another option that can rapidly lower cortisol levels and is particularly useful in acute settings (60). Etomidate, an intravenous anesthetic agent, also inhibits 11β-hydroxylase and can be administered as a continuous infusion in critically ill patients with severe hypercortisolism, offering rapid and titratable control (61). More recently, osilodrostat, a potent and selective 11β-hydroxylase inhibitor approved for Cushing disease, has shown promise in ECS, though data are limited (62). Mitotane, an adrenolytic agent that disrupts mitochondrial function in adrenal cortical cells, is effective but has a slow onset of action and significant side effects, including neurotoxicity and gastrointestinal disturbances (63). It is more commonly used in adrenocortical carcinoma but may be considered in refractory ECS (64,65). Glucocorticoid receptor antagonists, such as mifepristone, do not lower cortisol levels but block its peripheral effects, making them useful for managing hyperglycemia and psychiatric symptoms (66,67). However, they can exacerbate hypokalemia and are contraindicated in pregnancy (68). Pasireotide, a multi-receptor somatostatin analog, may reduce ACTH secretion in some neuroendocrine tumors, particularly carcinoids, but its efficacy in SCLC is limited due to lower somatostatin receptor expression (69, 70). Novel agents targeting the molecular pathways of cortisol synthesis or tumor growth are under investigation, including levoketoconazole and targeted therapies based on tumor genomics (71). Concurrent oncologic treatment is paramount. For SCLC-associated ECS, platinum-based chemotherapy (e.g., cisplatin or carboplatin combined with etoposide) is the standard first-line therapy (72). Response to chemotherapy often correlates with reduction in ACTH and cortisol levels, and rapid control of the tumor can lead to significant clinical improvement (67). Immunotherapy with immune checkpoint inhibitors (e.g., atezolizumab, durvalumab) has emerged as a standard component of first-line treatment for extensive-stage SCLC and may offer durable responses in a subset of patients (73,74). In bronchial carcinoids, which are less responsive to conventional chemotherapy, treatment options include somatostatin analogs (e.g., octreotide, lanreotide) for symptom control and tumor stabilization, peptide receptor radionuclide therapy with lutetium-177 DOTATATE for somatostatin receptor–positive tumors, and targeted therapies such as everolimus (an mTOR inhibitor) (75,76). Radiation therapy may be prescribed for local control or palliation of symptoms (77).

Prognosis of lung cancer–induced ECS

The prognosis of patients with lung cancer–induced ECS is generally poor, particularly in those with SCLC, where median survival is often less than one year from diagnosis of ECS (4,6). The severity of hypercortisolism itself contributes to morbidity and mortality through complications such as infections, thromboembolism, cardiac arrhythmias (from hypokalemia), and metabolic derangements (78,79). Early recognition and aggressive management of cortisol excess can improve quality of life and potentially extend survival by enabling patients to tolerate oncologic therapies (56). In contrast, patients with bronchial carcinoid–associated ECS have a more favorable prognosis, especially if the tumor is localized and completely resected, with long-term survival possible

(53,80). Critical care considerations are often necessary in the acute management of severe ECS (81). Patients may present in a hypercortisolemic crisis characterized by extreme hyperglycemia, severe hypokalemia, hypertension, and altered mental status (12). Intensive monitoring of electrolytes, glucose, and cardiovascular status is essential (82,83). Intravenous fluids, insulin infusion, and aggressive potassium and magnesium repletion are frequently required (17,84). Etomidate infusion can be initiated in the ICU setting to rapidly suppress cortisol production while definitive oncologic therapy is planned (61,85). Glucocorticoid withdrawal must be carefully managed post-treatment, as abrupt cessation of cortisol excess can lead to adrenal insufficiency, especially after tumor resection or effective chemotherapy (86,87).

Conclusion

Paraneoplastic hypercortisolism caused by ectopic ACTH secretion from lung cancers represents a serious endocrine disorder known as ECS. This condition arises when neuroendocrine tumor cells within the lung autonomously produce ACTH, independent of normal hypothalamic-pituitary regulation. The excess ACTH stimulates the adrenal cortex to hyper-secrete cortisol, resulting in systemic metabolic abnormalities such as severe hypertension, hypokalemia, hyperglycemia, muscle wasting, and immunosuppression. The diagnosis of ectopic ACTH syndrome requires a multifaceted approach. Biochemical tests reveal markedly elevated cortisol and ACTH levels coupled with a lack of suppression in dexamethasone suppression testing, indicative of ACTH production outside the pituitary. Radiologic imaging is essential to identify and localize the primary neuroendocrine lung tumor, often SCLC or large cell neuroendocrine carcinoma. Histopathologic confirmation from biopsy specimens showing ACTH immunoreactivity provides definitive diagnosis. Management of paraneoplastic hypercortisolism involves a dual strategy. Control of cortisol excess is pursued using steroidogenesis inhibitors such as ketoconazole, metyrapone, or etomidate, which block adrenal cortisol synthesis, along with mineralocorticoid receptor antagonists like spironolactone to counteract hypokalemia and hypertension. Simultaneously, treatment targeting the underlying lung malignancy, including chemotherapy and possibly radiotherapy, is critical to reduce ectopic ACTH production. Despite these interventions, the prognosis is generally poor, particularly in advanced SCLC due to aggressive tumor behavior and metabolic complications. Prompt recognition and aggressive multidisciplinary treatment are imperative to mitigate morbidity and improve survival outcomes.

Authors' contribution

Conceptualization: Mohammad Memarian.
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Funding acquisition: Mohammad Memarian.
Investigation: Masoume Bitaraf.
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Writing–original draft: Masoume Bitaraf, Mohammad Memarian.
Writing–review and editing: Masoume Bitaraf, Mohammad Memarian.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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