Ectopic Cushing's Syndrome as the First Presenting Sign of Small Cell Lung Carcinoma

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Background

Endocrine paraneoplastic syndromes occur when tumors acquire the ability to produce bioactive substances unrelated to their tissue of origin. We discuss the case of a patient who presented with ectopic Cushing's syndrome (CS) as the first manifestation of small cell lung carcinoma (SCLC).

Case Presentation

A 67-year-old man with a 5 pack-year smoking history presented with **several days of generalized weakness and mild confusion** as noted by his wife. He denied fever, chills, night sweats, weight loss, and shortness of breath.

Vital signs were notable for **new hypertension** to 144/81. Physical exam was remarkable only for jaundice and bruising. Cushingoid features were absent.

Lab studies demonstrated **potassium 1.9 mEq/L**, **venous pH 7.65**, venous pCO2 48 mmHG, **bicarbonate 45 mEq/L**, creatinine 1.30 mg/dL (from baseline 1), **glucose 231 mg/dL**, AST 58 IU/L, ALT 77 IU/L, total bilirubin 6.4 mg/dL, **WBC 17.4 x10^9/L**, hemoglobin 15.9 g/dL, and platelets 104 x10^9/L.

Given his severe hypokalemia and metabolic alkalosis, endocrine testing was performed **(Table 1)**.

Study	Value	Reference Range	Interpretation
Midnight cortisol (serum)	>75 µg/dL	<50 µg/dL	↑
ACTH	380 pg/mL	7.2 - 63.3 pg/mL	↑
Aldosterone	8.5 ng/dL	<16 ng/dL (supine)	↓ / —
AM cortisol, low-dose dexamethasone test	>150.0 µg/dL	0.0 - 5.0 µg/dL	**Cortisol levels not suppressed**
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Table 1: *Endocrine testing*

This confirmed the diagnosis of ectopic Cushing's syndrome. Computed tomography of the chest, abdomen, and pelvis revealed a large mediastinal mass compressing the mainstem bronchus, mediastinal lymphadenopathy, innumerable hepatic lesions, and a left adrenal lesion, interpreted as a metastasis rather than a primary tumor **(Figure 1)**. Brain MRI was negative for pituitary adenoma. A liver biopsy revealed metastatic SCLC. Spironolactone and ketoconazole were started. The patient's AM cortisol level decreased to 102.6 µg/dL, and his metabolic abnormalities normalized. However, shortly after initiation of palliative carboplatin/etoposide, he passed away after developing aspiration pneumonia.

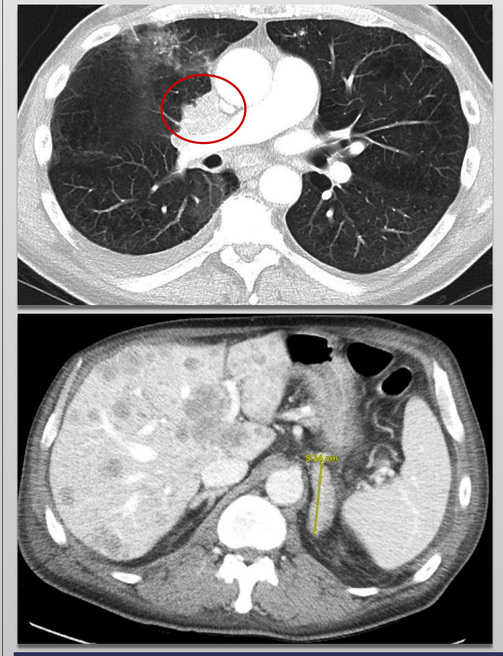


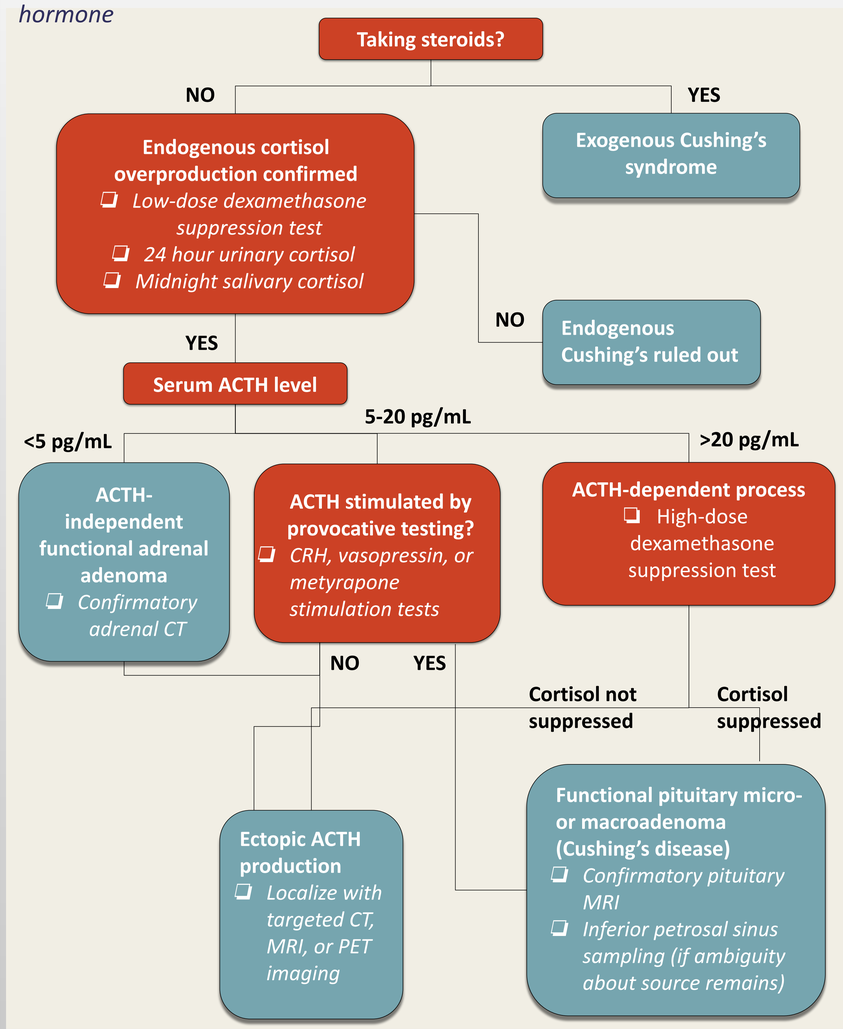
Figure 1a: *Chest CT demonstrating a 6.9 right perihilar/mediastinal mass (circled) compressing the right pulmonary artery and mainstem bronchi with additional lymphangitic carcinomatosis of the right upper lobe.*

Figure 1b: *Abdominal CT demonstrating extensive hepatic metastases. The left adrenal gland is enlarged up to 5.34cm and heterogeneously enhancing, concerning for metastatic disease.*

Discussion

5-10% of CS cases are caused by ectopic adrenocorticotropic hormone (ACTH) release. SCLC and neuroendocrine tumors are most commonly implicated. Aggressive cancers produce ACTH at much higher rates than pituitary adenomas, leaving little time for the classic exam findings of Cushing's syndrome to develop. **Many patients instead present with features of severe acute hypercortisolism, including hyperglycemia, leukocytosis, hypertension, hypokalemia, and metabolic alkalosis.** The last three are driven by activation of the mineralocorticoid receptor by excess cortisol, leading to pseudohyperaldosteronism.

Figure 2: *Workup of suspected hypercortisolism. CRH: corticotropin-releasing hormone*



ACTH production is a poor prognosticator in SCLC, associated with more extensive disease, decreased response to first-line treatment, and infectious and cardiac complications. In addition to tumor-targeted therapy, **treatment should include steroidogenesis inhibitors such as ketoconazole and metyrapone to rapidly suppress cortisol to normal levels.**

References

Hayes, A. R., & Grossman, A. B. (2018). The Ectopic Adrenocorticotropic Hormone Syndrome: Rarely Easy, Always Challenging. Endocrinol Metab Clin North Am, 47(2), 409-425. https://doi.org/10.1016/j.ecl.2018.01.005
Alexandraki, K. I., & Grossman, A. B. (2010). The ectopic ACTH syndrome. Rev Endocr Metab Disord, 11(2), 117-126. https://doi.org/10.1007/s11154-010-9139-z
Dimitriadis, G. K., Angelousi, A., Weickert, M. O., et al. (2017). Paraneoplastic endocrine syndromes. Endocr Relat Cancer, 24(6), R173-R190. https://doi.org/10.1530/ERC-17-0036
Sarlis, N. J., Chanock, S. J., & Nieman, L. K. (2000). Cortisolemic indices predict severe infections in Cushing syndrome due to ectopic production of adrenocorticotropin. J Clin Endocrinol Metab, 85(1), 42-47. https://doi.org/10.1210/jcem.85.1.6294