

An Uncommon case of Cushing's Syndrome: Ectopic ACTH secretion

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Cushing's syndrome (CS) is the end result of long-standing exposure to increased levels of cortisol. This can be divided into two groups: exogenous and endogenous hypercortisolaemia. The former is usually the result of prolonged exposure to synthetic glucocorticoids. On the other hand, endogenous causes result from increased release of cortisol by the adrenal glands and can be ACTH-dependent or ACTH-independent. 80% of endogenous CS is due to ACTH-dependent cortisol excess secondary to a pituitary adenoma [1]. The remaining endogenous causes of CS are due to ACTH-independent adrenal causes (adrenal hyperplasia, adrenal adenomas, and adrenal carcinomas), followed by unknown sources, and ectopic ACTH secretion by neoplasms. The authors present a case of ectopic ACTH-dependent hypercortisolism due to an aggressive metastatic neuroendocrine tumour.

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CASE PRESENTATION

A 61-year-old gentleman presented to the accident and emergency department with mild haemoptysis and dyspnoea. The patient also complained of weight gain, increasing waist circumference, and lower limb swelling. Baseline parameters showed that the patient was hypertensive (BP: 170/60 mmHg). Physical examination noted the presence of cushingoid features. These included centripetal obesity, Cushingoid facies, easy bruising, peripheral oedema, and skin atrophy. Hyper-pigmentation was also noted.

Past medical history included hypertension which was previously controlled by amlodipine 10mg daily. He had no known drug allergies and was a lifelong heavy smoker.

INVESTIGATIONS

Laboratory investigations revealed the presence of hypokalemia of 2.83 mmol/l (normal range: 3.5-5.1 mmol/l) and hypernatremia of 154 mmol/l (normal range: 135-145 mmol/l). He was hyperglycemic with an HbA1c of 7%. The patient's complete blood count showed neutrophilia. On presentation, the patient was also noted to have biochemical jaundice with a bilirubin of 38.6 micromol/L and slight deranged hepatic enzymes with a gamma-glutamyl transferase of 145 U/l (normal range: 8-61 U/l) and an alanine aminotransferase of 105 U/l (normal range: 5-41 U/l).

In light of the above presentation, especially the presence of haemoptysis, the patient underwent a

computed tomography (CT) scan of his thorax, abdomen, and pelvis. This revealed the presence of diffuse pulmonary and liver lesions. The latter lesions were suggestive of metastasis. The CT scan also noted coarse structure of the left femoral head indicative of avascular necrosis.

In view of the patient's presentation and the CT findings, the clinical suspicion for endogenous hypercortisolism was high. Hence, a 9 am cortisol was taken and was found to be elevated at 2512 nmol/l (normal range: 145-619 nmol/l). A 24-hour urinary free cortisol was also high at 3236 nmol/24h (normal range: 57.7- 806.8 nmol/24h). ACTH levels were found to be inappropriately elevated.

Furthermore, there was non-suppressibility to both low-dose and high-dose dexamethasone suppression tests (DST).

Pituitary Magnetic Resonance imaging (MRI) excluded pituitary causes. The CT findings, absence of pituitary pathology on MR, and failure to suppress to high dose DST were more indicative of ectopic ACTH secretion. A Magnetic Resonance Cholangio-Pancreatography (MRCP) was performed for further characterization of the liver pathology. This showed the presence of multiple bilobar hypovascular lesions. These were biopsied and histopathology was consistent with a metastatic high-grade neuroendocrine carcinoma favouring a lung primary (**Figure 1**). In view of this, plasma Chromogranin A was taken and found to be elevated at 250mcg/l. 24-hour urinary 5-hydroxyindoleacetic acid level was within normal limits.

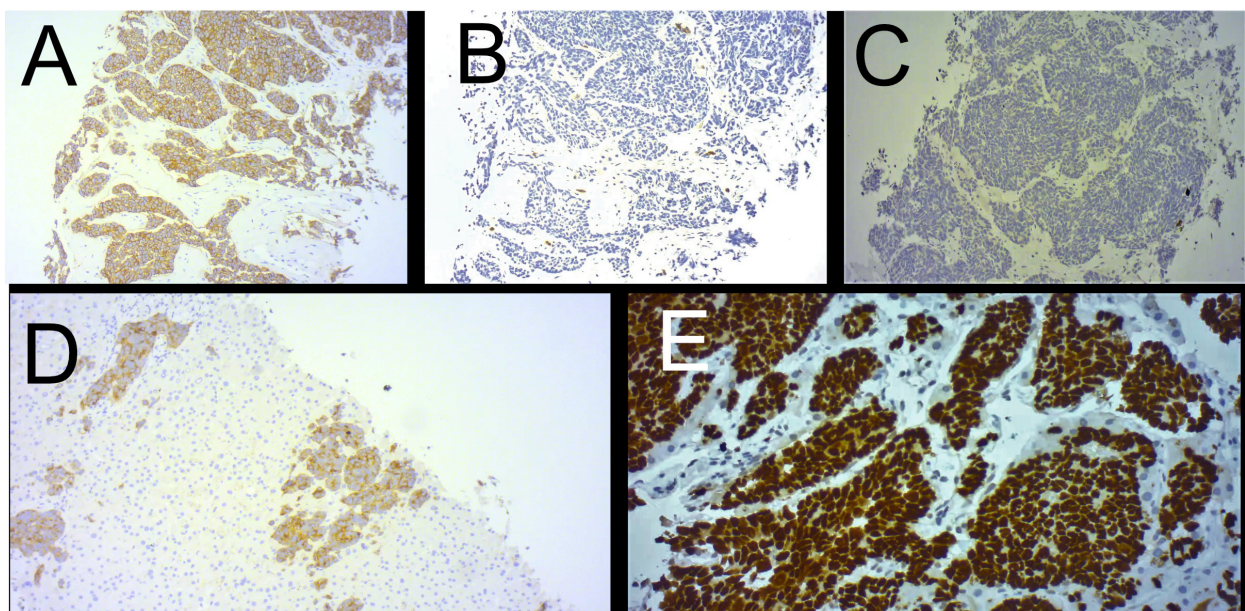


Figure 1 Liver core biopsies show infiltration of liver parenchyma by a tumour composed of solid nests of cells having a high nuclear-to-cytoplasmic ratio, hyperchromatic nuclei with some nuclear moulding, and brisk mitotic activity. On immunohistochemistry, the tumour cells show strong and diffuse positivity for CD56, synaptophysin, and TTF-1 and very focal CK7 positivity. CK20 is negative. These features are in keeping with a metastatic high-grade neuroendocrine carcinoma, likely from a lung primary. A) H&E stain B) CK7 stain C) CD56 stain D) Synaptophysin E) TTF-1 stain

Table 1 *Types of NET, hormone released, and syndrome associated with the tumour²*

Tumour	Hormone released	Syndrome
ACTHoma	ACTH	Cushing's Syndrome
Atypical carcinoid	5-Hydroxytryptophan, histamine	Atypical Carcinoid
Carcinoid	Serotonin, tachykinin, prostaglandins	Carcinoid
Insulinoma	Insulin, pro-insulin	Whipple's trial
Gastrinoma	Gastrin	Zollinger Ellison Syndrome
Glucagonoma	Glucagon	4D Syndrome
Somatostatinoma	Somatostatin	Somatostatinoma syndrome
VIPoma	Vasoactive intestinal peptide (VIP)	Verner-Morrison syndrome

MANAGEMENT

Electrolyte derangement was aggressively treated alongside his hypertension and diabetes mellitus.

Oncology input was sought and in view of advanced disease, the patient was not deemed to be a candidate for surgery. Medical treatment for endogenous ectopic ACTH production involved metyrapone. Ketoconazole was contraindicated in view of deranged liver function tests.

DISCUSSION

Our case represents a patient who suffered from ACTH-dependent CS secondary to ectopic ACTH production from a lung NET.

NET may be functional or non-functional. Functional NET compromises a group of malignancies which are responsible for the secretion of several biopeptides (Table 1).² These tumours are most commonly associated with the thoracic cavity and gastrointestinal tracts. The prevalence of ectopic ACTH secretion in patients with NET is around 3.2%.³

Our patient presented with CS as a result of high circulating levels of cortisol. Cortisol is a catabolic hormone produced by the zona fasciculata in the adrenal cortex. 90% of this cortisol is transported bound to cortisol binding proteins.¹ The causes of CS can be appreciated in Figure 2.^{4,5}

The initial assessment should include one of the following confirmatory tests: urinary free cortisol (two measurements), late-night salivary cortisol (at least two measurements), 1 mg overnight dexamethasone suppression test, or the longer low-dose DST (2mg/day for 48 hours). If any of the above tests are abnormal, the use of another confirmatory

test is recommended.⁶ Low-dose DST followed by corticotropin-releasing hormone (CRH) stimulation test may be of value in differentiating between CS and pseudo-CS. This involves the administration of 100mcgs of CRH following a 48hour low-dose DST. A cortisol level above 38nmol/L, measured 15 minutes after administration of CRH was found to predict CS.⁷

The next step in investigating CS would be to measure ACTH levels. If levels are low, ACTH-independent causes should be suspected. On the other hand, if ACTH levels are high or inappropriately normal, then one should investigate for ACTH-dependent causes. If the pituitary scan is normal, an ectopic etiology should be considered as in our case. Establishing the ectopic cause via directed CT scanning may be helpful.⁷ In patients with ACTH-dependent CS where no clear source is identified, bilateral inferior petrosal sinus sampling is recommended.⁷ In our case, the longstanding history of smoking and the new-onset haemoptysis pointed towards lung pathology which was confirmed on CT and histopathology results.

Treating ectopic ACTH syndrome (EAS) may be challenging. The Endocrine Society Clinical Practice Guideline; Treatment of Cushing's Syndrome recommends localizing and resecting the ectopic ACTH-secreting tumour with node dissection as appropriate as a first-line treatment option.⁸

Furthermore, Miller CA & Ellison EC also suggest that in patients with metastatic neuroendocrine tumours limited to the liver, one can consider resection or cryoablation of the liver metastases, or even liver transplantation following resection of the primary tumour.⁹

In patients with EAS for whom surgery is not possible due to metastatic nonresectable tumours or an occult tumour or in those who are severely ill, medical

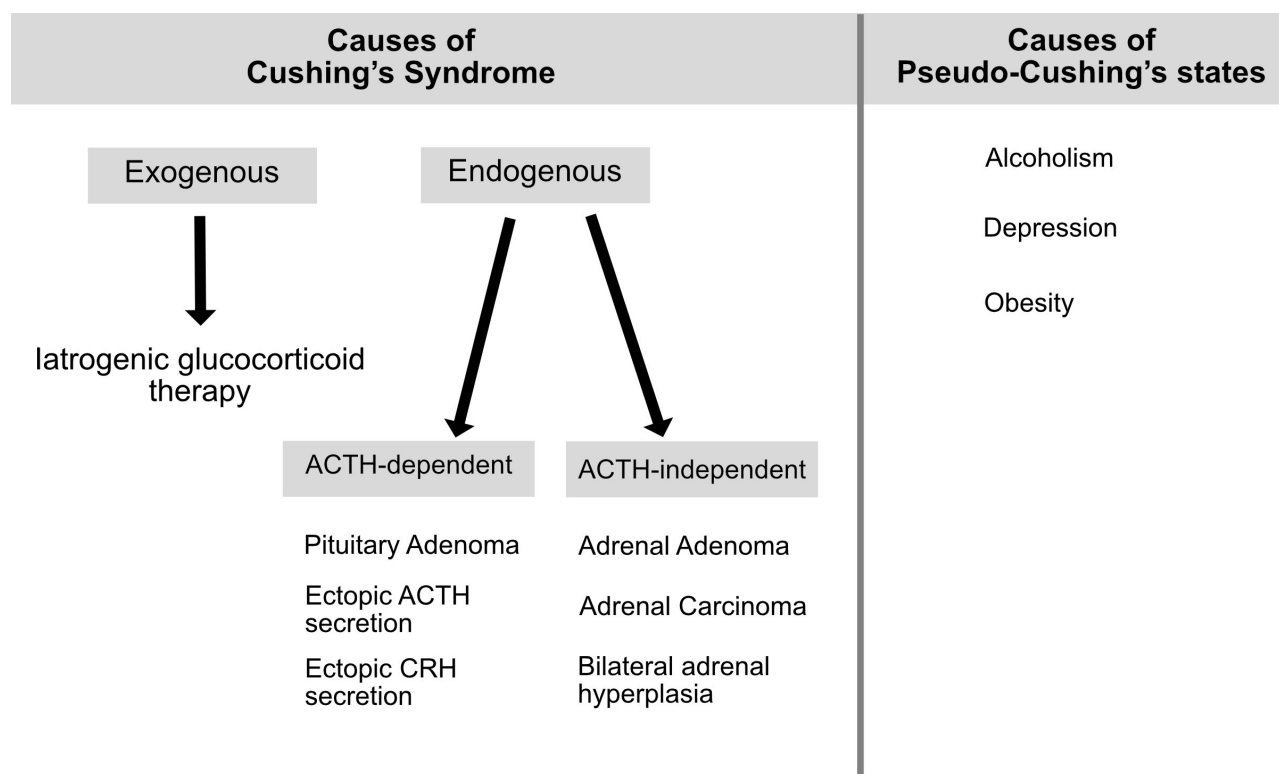


Figure 2 Causes of Cushing's syndrome and pseudoCushing's states

therapy with steroidogenesis inhibitors can serve as primary treatment. These include; ketoconazole, metyrapone and etomidate.⁸

Recent preliminary data suggest that a new 11-hydroxylase inhibitor known as LCI699 may have a promising potential role in patients with EAS. However, the latter requires confirmation in clinical trials with a significant number of patients with EAS.¹⁰

In an expert operational opinion, slow-acting cortisol-lowering drugs such as mitotane and mifepristone may also have a role in patients with EAS.¹⁰ Of note, physicians need to be careful when prescribing mitotane in addition to other medications including anti-neoplastic agents, as mitotane has a potent and long-lasting inducing effect on the enzyme CYP3A4. This can lead to clinically relevant drug-drug interactions.¹¹

Both the Endocrine Society guideline and the expert opinion, mention the use of agents that inhibit ACTH

secretion by the NET. These include somatostatin analogues such as octreotide, the dopamine-2 receptor agonist cabergoline and tyrosine kinase inhibitors such as vandetanib, sorafenib and sunitinib.^{8,10}

In occult or metastatic EAS or in patients with very severe ACTH-dependent CS who cannot be promptly controlled by medical therapy, the Endocrine Society Clinical Practice Guideline also suggests bilateral adrenalectomy.¹⁰ Albeit an effective treatment option, bilateral adrenalectomy is weighed down by significant perioperative mortality and morbidity rates, the risk of developing Nelson's syndrome, and other long-term complications that can result in reduced life expectancy.¹² The possibility of Nelson's syndrome in adults ranges from 8-47%.¹³

In conclusion, this case highlights the need for a high degree of clinical suspicion as well as the diagnostic investigations required for establishing the aetiology of CS.

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