Pulmonary embolism as the presenting symptom and a confounder in ACTH-secreting bronchial carcinoid

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Summary

Ectopic ACTH-secreting pulmonary neuroendocrine tumors are rare and account for less than 5% of endogenous Cushing's syndrome cases. We describe an unusual case of metastatic bronchial carcinoid tumor in a young woman presenting with unprovoked pulmonary emboli, which initially prevented the detection of the primary tumor on imaging. The source of ectopic ACTH was ultimately localized by a Gallium-DOTATATE scan, which demonstrated increased tracer uptake in a right middle lobe lung nodule and multiple liver nodules. The histological diagnosis was established based on a core biopsy of a hepatic lesion and the patient was started on a glucocorticoid receptor antagonist and a somatostatin analog. This case illustrates that hypercoagulability can further aggravate the diagnostic challenges in ectopic ACTH syndrome. We discuss the literature on the current diagnosis and management strategies for ectopic ACTH syndrome.

Learning points:

- In a young patient with concurrent hypokalemia and uncontrolled hypertension on multiple antihypertensive agents, secondary causes of hypertension should be evaluated.
- Patients with Cushing's syndrome can develop an acquired hypercoagulable state leading to spontaneous and postoperative venous thromboembolism.
- Pulmonary emboli may complicate the imaging of the bronchial carcinoid tumor in ectopic ACTH syndrome.
- Imaging with Gallium-68 DOTATATE PET/CT scan has the highest sensitivity and specificity in detecting ectopic ACTH-secreting tumors.
- A combination of various noninvasive biochemical tests can enhance the diagnostic accuracy in differentiating Cushing's disease from ectopic ACTH syndrome provided they have concordant results. Bilateral inferior petrosal sinus sampling remains the gold standard.

Background

Endogenous Cushing's syndrome (CS) has an incidence of two to three cases per one million persons per year and is associated with multisystem morbidity and mortality. This includes myocardial infarction, stroke, fractures, infections, peptic ulcers and venous thromboembolism (1, 2). The most common cause of non-iatrogenic CS is an ACTH-secreting pituitary adenoma, also known as Cushing's disease (CD), followed by adrenal tumors or hyperplasia (1). Ectopic ACTH syndrome (EAS) from a non-pituitary tumor comprises 10% of CS, of which the most common is small-cell lung cancer (27%) followed by pulmonary carcinoids (21%) (3). Bilateral inferior petrosal sinus sampling (BIPSS) can be used to exclude a pituitary source, but localizing the source of ectopic ACTH can be challenging.
ACTH is often difficult. Here we describe a case of an ACTH-secreting metastatic bronchial carcinoid in which spontaneous pulmonary emboli at first interfered with the visualization of the lung lesion and further complicated the diagnosis. Because 73% of patients harboring well-differentiated neuroendocrine tumors (NETs) with distant metastasis die within 5 years, timely identification and source localization are important (4).

Case presentation

A 25-year-old woman presented to the emergency room with dyspnea on exertion and difficulty with ambulation from worsening bilateral lower extremity edema. Seven months prior to her presentation, the patient had seen her internist for new-onset lower extremity edema and had been diagnosed with hypertension. Lisinopril was prescribed by her internist and titrated to maximum dose. Potassium supplementation was also initiated for persistent hypokalemia. A renal Doppler ultrasound was negative for renal artery stenosis. The patient was subsequently referred to a nephrologist who discontinued her lisinopril and started furosemide. The patient took furosemide intermittently and also started taking a family member’s amlodipine, without normalization of her blood pressure.

When the patient presented to the hospital emergency room, she denied symptoms of cough, chest pain or non-exertional dyspnea. She noticed worsening facial acne and had been amenorrheic for the previous 3 months. She denied family history of autoimmune disease, endocrinopathies or thromboembolic disease. Her physical examination was notable for tachycardia, facial plethora, dorsocervical fullness, purple striae over bilateral forearms and abdomen, central obesity and bilateral pitting lower extremity edema. Laboratory evaluation revealed a potassium of 2.2 mmol/L (normal: 3.3–5.1), glucose of 238 mg/dL (normal: 70–115) and a D-dimer level of 529 ng/mL (normal: 0–230). A lower extremity ultrasound showed no deep venous thromboses.

However, a computed tomography angiogram (CTA) of the chest demonstrated bilateral subsegmental pulmonary emboli (Fig. 1A).

Investigation

Given her constellation of signs and symptoms, the endocrinology service was consulted and a workup for hypercortisolism ensued. Baseline 08:00 h morning cortisol and 24-h urine-free cortisol (UFC) were found to be elevated at 32 µg/dL (normal: 3.7–19.4) and 1335 µg/day (normal: ≤45), respectively. Repeat 24-h UFC was again elevated at 2856 µg/day. A low-dose (1 mg) dexamethasone suppression test (LDDST) resulted in a morning cortisol of 29.1 µg/dL (normal: <5). Adrenocorticotropic hormone (ACTH) level was inappropriately normal at 82 ng/L.

Prolactin, IGF-1 and CRH levels were in normal range. LH and FSH levels were low. A hypercoagulable workup showed an increased Factor VIII level of 283% (normal: 46–191), von Willebrand Factor (vWF) activity of 368% (normal: 42–176), vWF ristocetin activity of
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For source localization, the patient first underwent pituitary magnetic resonance imaging (MRI) and a computed tomography (CT) of the abdomen with adrenal protocol, neither of which revealed evidence of any overt masses or nodules. A calcitonin level was checked at this point and was elevated to 59 pg/mL (normal: 0–5.1), which raised the possibility of EAS. Chromogranin A was elevated at 135 ng/mL (normal 0–95). During the search for an ectopic lesion, a second read of the initial CTA of the chest resulted in the finding of a 1.4 cm by 1.3 cm lung mass in the anterior right middle lobe associated with a wedge infarct that had initially been attributed to pulmonary emboli (Fig. 1B). An attempt to characterize the right middle lobe lesion with FDG-positron emission tomography (PET) failed to demonstrate any metabolically active uptake in the area of interest. To further differentiate between a pituitary and an ectopic ACTH source, the patient underwent an 8 mg overnight high-dose dexamethasone suppression test (HDDST) in which morning cortisol level failed to suppress (24.1 µg/dL). A CRH stimulation test yielded a maximum cortisol increase of 7.2% and a maximum ACTH increase of 12.6% from baseline, which were suggestive of EAS rather than CD. Given the possibility of a lung neuroendocrine tumor, the patient underwent a Gallium-68 DOTATATE PET/CT (Ga 68 PET/CT) which showed a 1.6 cm by 3.2 cm nodular mass-like opacity in the right middle lobe with significantly increased radiotracer uptake as well as and multiple hypodensities within the right lobe of the liver with increased uptake (Fig. 2A and B).

An ultrasound-guided biopsy of a hepatic lesion was performed. Histologic sections of the biopsy showed the liver parenchyma infiltrated by an epithelioid neoplasm with a nested architecture, composed of cells with a moderate amount of amphophilic cytoplasm, relatively uniform, round nuclei with granular chromatin (Fig. 3A). The tumor cells were immunohistochemically positive for pankeratin (AE1/AE3), chromogranin and synaptophysin (Fig. 3B and C). Additionally, there was patchy ACTH expression on the immunostain suggestive of ectopic secretion. No cytologic atypia or necrosis were present. There were less than 1 mitosis per 2 mm². The immunohistochemical stain for Ki67 revealed an index of proliferation of less than 2%, confirmatory of a grade 1 neuroendocrine tumor (Fig. 3D). The morphology and the immunophenotype, in conjunction with imaging, supported a lung primary.

Treatment

The patient was started on heparin drip for anticoagulation and then transitioned to rivaroxaban. For new-onset diabetes, she was started on metformin and received insulin during her hospital stay. For blood pressure control, amlodipine was continued and lisinopril was resumed.

She was evaluated by thoracic surgery and hepatobiliary surgical oncology and deemed not a surgical candidate. Palliative and symptomatic treatment was initiated. She was discharged on oral mifepristone 300 mg

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daily and subcutaneous octreotide injections every 8 h with plans to switch to long-acting lanreotide. She was continued on metformin for diabetes and discharged with spironolactone, lisinopril and amlodipine for hypertension.

Outcome and follow-up

At her 1-month follow-up, the patient reported a 3 pound weight loss, nausea and fatigue with mifepristone. Her hypertension and hypokalemia abated and diabetes was well controlled on metformin. The patient had been on the lowest dose (300 mg daily) of mifepristone approved by the U.S. Food and Drug Administration (FDA) for treatment of CS and no dosage reduction was made. At 2-month follow-up, patient’s symptoms of nausea and fatigue improved, ACTH value decreased to 38 ng/L (originally 89) and chromogranin A decreased to 39 ng/mL (originally 153). At 6-month follow-up, all medication side effects have been resolved. Her 24-h UFC value normalized to 10.7 µg/day (normal: ≤ 45), likely reflecting the effect of somatostatin analogs in suppressing ACTH secretion. She has been referred to a liver surgery program at another center for a secondary evaluation of possible surgical options.

Discussion

Our patient’s presentation with poorly controlled hypertension and hypokalemia despite antihypertensive agents was suspicious for a secondary cause of hypertension. In such patients, use of a mineralocorticoid receptor antagonist represents a more rational approach given the pathophysiological mechanism and might have been considered earlier in management. The diagnosis of CS was supported by her clinical signs, and was established by two markedly elevated 24-h UFC values and a positive LDDST. The patient’s inappropriately normal ACTH narrowed the differential to a pituitary or ectopic source. Her presentation with spontaneous pulmonary embolism is atypical, but hypercoagulability is a known complication of hypercortisolism. Untreated CS can be associated with increased venous thromboembolism risk due to both activation of the coagulation cascade and an impaired fibrinolysis (5). Increased levels of Factor VIII, vWF antigen and vWF ristocetin activity and reduced fibrinogen levels were present in our patient.

The challenging aspect of this case was distinguishing CD from EAS since surgical resection of the causal lesion is generally the first-line approach. Our case is unique in that the presenting pulmonary embolus confounded the interpretation of initial imaging studies and prevented the identification of an ectopic source. BIPSS is the gold standard to differentiate between pituitary-dependent CS and EAS. Dynamic testing with CRH and HDDST can be useful when results of both tests point to the same diagnosis. However, in up to 65% of patients with ACTH-dependent CS results of these tests are discordant, in which case BIPSS is still needed to establish the diagnosis (6). Fortunately, our patient was able to bypass BIPSS because specific concordant biochemical and radiological studies allowed us to establish the definitive diagnosis. Both of these points are further discussed below.

For biochemical workup, a normal ACTH does not rule out CD or EAS as up to 32% of patients with EAS and 37% with CD may have normal ACTH levels (7).
An elevated calcitonin raised our suspicion for EAS given serum calcitonin is elevated in 44–69% of patients with EAS, as opposed to being in normal range in CD (8). The failure of cortisol to suppress appropriately on the HDDST also argued against CD. In a retrospective Italian multicenter study of 426 patients, cortisol suppression of >80% had a 56% sensitivity and a 100% specificity for CD (9).

The biochemical study in this case which yielded the highest sensitivity and specificity was the CRH stimulation test. In EAS, the ACTH and cortisol levels are usually not altered by the CRH administration as ectopic tumors cells tend to be poorly responsive to CRH. At least a 35% rise in ACTH compared to baseline has a 93% sensitivity and 100% specificity for CD. A 20% increase in cortisol has a sensitivity and specificity of 91 and 88%, respectively (10). Additionally, it has also been shown that the combination of the CRH stimulation test and the HDDST enhances diagnostic accuracy. In one Spanish study of 73 patients with CS, combined HDDST-CRH had a 74% negative predictive value for CD and 100% specificity, while HDDST or CRH stimulation alone had negative predictive value of 29 and 42%, respectively (9). The negative results on both two tests further increased our suspicion for EAS.

Another essential tool in source localization in CS is imaging. The patient’s CT of the abdomen with adrenal protocol did not reveal any mass lesion within the adrenal glands, making an adrenal source unlikely. A brain MRI performed to assess the pituitary gland was also negative, but in 30–50% of CD patients, pituitary microadenomas are not visible on MRI (11). In the current literature, EAS tumors were localized by CT scan in 66.2% of cases, MRI in 51.5% and FDG-PET/CT in 51.7% of cases. The gold standard for imaging detection of EAS is Ga 68 PET/CT, which has a sensitivity of 81.8% and specificity of 100% (12). On initial assessment, the patient was found to have pulmonary emboli affecting the lower lobes and a segmental wedge infarct in the right middle lobe. On further assessment, the wedge infarct was actually found downstream from a 2 cm pulmonary nodule, rather than an expected pulmonary embolus. Unfortunately, given the patient’s coagulation status and the location of the nodule, the lesion was not amenable to direct biopsy.

The patient’s FDG-PET/CT scan showed nonspecific low level FDG uptake within the lung nodule, unsurprisingly given its sensitivity of 51.7%. Further evaluation with Ga 68 PET/CT demonstrated strong uptake of Ga-DOTATATE within the pulmonary nodule. Incidentally, multiple additional foci of Ga-DOTATATE uptake were noted in the liver, suspicious for metastatic disease. One of these liver lesions had previously been noted as a hypodensity on CT abdomen, but was indeterminate in isolation. The suspected liver metastases were amenable to ultrasound-guided core biopsy which ultimately led to a pathologic diagnosis of grade 1 bronchial carcinoid with metastasis in the liver.

Prognosis in patients with pulmonary carcinoid and distant metastases is poor regardless of tumor grade. According to a retrospective study at MD Anderson in 2017, the median overall survival is 12 months (13). Hormonally, CS traditionally has been managed with medications that inhibit adrenal steroid production, such as ketoconazole, but tolerance is limited due to gastrointestinal side effects, significant hepatotoxicity and adrenal insufficiency. Mifepristone, a glucocorticoid receptor antagonist, was selected over a steroid synthesis inhibitor in our patient because of its more rapid onset of action in ameliorating the symptoms of CS (14). It is also approved by the U.S. FDA to control cortisol-induced hyperglycemia in patients with CS who have diabetes mellitus and are not surgical candidates. One significant disadvantage is mifepristone does not lower the absolute level of cortisol and can actually increase it, and so hormonal measurements do not reflect the glucocorticoid receptor activity. Patients may be at risk for adrenal insufficiency at excessive doses. Blood pressure and potassium levels need to be monitored while on mifepristone. For management of malignancy, surgery remains the treatment of choice for pulmonary carcinoids. Per European Neuroendocrine Tumor Society Expert Consensus for typical and atypical pulmonary carcinoids, surgery can be considered in patients with limited sites of metastatic disease with curative intent (15). Complete resection of liver metastases was shown to increase 5-year overall survival to 70%. Adjunctive antitumor therapies including transarterial chemoembolization, radiofrequency ablation and peptide receptor radionuclide therapy may also be considered (15). Finally, somatostatin analogs are used for palliative tumor control and have been shown to induce stabilization in 30–70% of patients with well-differentiated NET (16).

Our case illustrates that while no single test is completely sensitive or specific in EAS, combinations of studies predicated on clinical pretest probability can substantially enhance diagnostic accuracy. Despite the numerous limitations and often steep costs of biochemical and radiologic studies for this rare disorder,
making a timely diagnosis is critical for the optimal clinical outcome.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

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