An Unusual Presentation of Adrenocortical Carcinoma (ACC): Panic Attacks and Psychosis

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Patient: Female, 52-year-old
Final Diagnosis: Adrenocortical carcinoma
Symptoms: Flushing • hot flashes • panic attack • psychosis
Medication: —
Clinical Procedure: —
Specialty: Endocrinology and Metabolic

Objective: Unusual clinical course
Background: Adrenocortical carcinoma (ACC) is a very rare disease, with an incidence of 1.02 per million population per year. The most commonly secreted hormone in ACC is cortisol, often presenting as a rapidly progressive Cushing syndrome (CS). We describe a case of ACC with an unusual presentation, mainly with psychiatric manifestations, including panic attacks and hallucinations.

Case Report: A 52-year-old woman presented with episodes of acute anxiety, hallucinations, palpitations, hot flashes, gastrointestinal upset associated with paroxysmal hypertension, tachycardia, and flushing for 1 week. The initial workup was aimed at ruling out causes of acute psychosis and/or anxiety such as substance use, and organic diseases such as pheochromocytoma (PCC). Our initial suspicion of PCC was ruled out based on the negative serum and urinary metanephrines (MN) and normetanephrines (NMN). Recurrent metabolic alkalosis and hypokalemia despite fluid and potassium supplementation prompted us to work up for hyperaldosteronism. Her renin level was elevated and the aldosterone level was appropriately suppressed. Elevated cortisol, positive dexamethasone (DXM) suppression test, low adrenocorticotropic hormone (ACTH), imaging revealing an adrenal mass, and postoperative histology confirmed the diagnosis of cortisol-producing ACC.

Conclusions: It is essential to recognize psychiatric presentations of CS to achieve early diagnosis and prevent mortality and morbidity. Panic attacks, a common presentation of CS, can present with features mimicking pheochromocytoma (PCC), including palpitations, sweating, tachycardia, and paroxysmal hypertension. A comprehensive work-up is warranted to reach a diagnosis, with a combination of hormonal levels, imaging, and histology.

Keywords: Adrenocortical Carcinoma • Cushing Syndrome • Panic Disorder • Pheochromocytoma

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Background

Adrenocortical carcinoma (ACC) is a very rare disease, with an incidence of 1.02 per million population per year in a population-based study in the United States [1]. Up to 60% of patients with ACC present with symptoms of adrenal steroid hormone excess [2]. The most commonly secreted hormone in ACC is cortisol, often presenting as a rapidly progressive Cushing syndrome [3,4]. We describe a case of ACC with an unusual clinical presentation, mainly with psychiatric manifestations, including panic attacks and hallucinations, associated with paroxysmal hypertension, tachycardia, flush, and hot flashes.

Case Report

History of Present Illness

Our patient was a 52-year-old woman who was brought in by Emergency Medical Services, accompanied by her sister due to acute episodes of anxiety and aggressive and bizarre behavior at home that started during the previous week. These episodes were accompanied by increased sweating, hot flashes, flushing, palpitations, and gastrointestinal upset, without any identifiable precipitating factor. She denied any prior similar episode in the past. She endorsed a 9-kg weight loss over the last 3-4 months. She denied headaches, visual changes, loss of consciousness, tremors, weakness, chest pain, shortness of breath, diarrhea, easy bruising, striae, arthralgia, and myalgia.

Past Medical History

Her past medical history was significant for recently diagnosed hypertension (weeks prior) and diabetes mellitus (DM) (months prior). She and her sister denied any personal or family history of psychiatric disorders (including mood disorders, psychotic disorder, substance use disorders, psychiatric hospitalizations, and suicide attempts). She had a surgical history of total abdominal hysterectomy and cholecystectomy years prior. Her family history included a father with diabetes mellitus, and renal cancer in another sister (now deceased). Her medications included lisinopril, metformin, and glimepiride. Glimepiride was switched to ertugliflozin following an episode of hypoglycemia. She denied alcohol use, smoking, or illicit drug use.

Physical Examination

Initial physical examination showed a temperature 37.2°C, a blood pressure of 135/86 mmHg, a heart rate of 115/min, a respiratory rate of 18/min, and oxygen saturation of 98% on room air. Body mass index (BMI) was 22.17 kg/m². The patient was alert and oriented to time, place, and person. She was anxious, tearful, and appeared to have intermittent visual hallucinations along with persecutory and psychotic delusions. Skin inspection revealed flushing of the face and the chest, without any visible lesions. The chest was clear on auscultation bilaterally, with normal heart sounds, a soft abdomen with mild epigastric tenderness, and no edema. She was placed on continuous telemetry for monitoring of her vital signs.

Laboratory Workup

An ECG showed sinus tachycardia (115 beats/min), with possible right atrial enlargement (RAE), and left ventricular hypertrophy (LVH) with repolarization changes (Figure 1). A comprehensive urine drug screen panel was negative. Laboratory findings are summarized in Table 1. Our differential diagnoses for leukocytosis, lymphopenia, and neutropenia included infection, autoimmune disease, Human Immunodeficiency Virus (HIV) infection, and hypercortisolism. Urinalysis was positive (positive leukocyte esterase, nitrites, leukocyturia, bacteriuria), so a urine culture was performed. Antinuclear antibodies (ANA) and anti-double stranded DNA (DsDNA) were negative and ruled out systemic lupus erythematosus. Hypokalemia and metabolic alkalosis prompted us to screen for causes of hyperaldosteronism. Further laboratory workup ruled out primary/secondary hyperaldosteronism and pheochromocytoma (Table 1). The diagnosis of CS was made based on elevated 24-h free urinary cortisol, elevated serum AM Cortisol at 37.9 mcg/dL, and positive dexamethasone (DXM) suppression test (inappropriate suppression of morning serum cortisol after 1 mg DXM administration: 30 ug/dL). ACTH level was low, indicating a peripheral cause of CS.

Imaging

A computed tomography (CT) scan of the head without contrast was unremarkable, with the exception of mild diffuse cerebral atrophy. A CT of the abdomen and pelvis showed a large adrenal heterogeneous mass with calcifications (Figure 2). Differential diagnoses for this mass included adrenal carcinoma, pheochromocytoma, or, less likely, lipid poor adenoma. CT of the chest with contrast revealed a 4-mm semisolid left lower lung lobe nodule and an 8-mm ground-glass nodule in the right upper lobe.

Treatment and Follow-Up

Prior to the diagnosis, the patient was medically managed with intravenous (i.v.) fluids and electrolytes repletion, trimethoprim-sulfamethoxazole (TMP-SMX) for urinary tract infection, amlopidine and lisinopril for hypertension, labetalol for tachycardia, insulin for DM, and antipsychotics. After the diagnosis of ACC was suspected based on the imaging and the hormonal panel, she was medically cleared for surgery and underwent a right adrenal tumor resection.
To prevent postoperative adrenal insufficiency, the patient received an initial dose of i.v. hydrocortisone (HC) 50 mg every 4 h on the surgery day, which was tapered down on postoperative days 1, 2, and 3 to 50 mg every 6, 8, and 12 h, respectively. On day 4, she received oral HC 50 mg at 8 AM, and 25 mg at 4 PM. She was discharged on the same day, and continued on oral HC 25 mg twice daily and potassium supplementation. The postoperative course was uncomplicated, with resolution of the psychiatric and cardiovascular symptoms. She was alert, calm, and oriented, with a normal blood pressure of 105/65 mmHg and heart rate of 74/min at follow-up.

Histology results available after 8 days were consistent with low-grade ACC with a free tumor margin. Tumor cells were positive for SF-1, Melan-A, and Inhibin and negative for INSM1 and chromogranin. A PET-CT scan showed no evidence of lymph node or bone metastasis, and revealed a mildly hypermetabolic pulmonary nodule and a right upper lobe ground-glass nodule without FDG uptake, both possibly neoplastic. She continues to follow up with Endocrinology, Cardiology, and Oncology. Further germline testing of the tumor is pending.

Discussion

Adrenocortical carcinoma (ACC) is a very rare disease, with an incidence ranging from 0.72 to 2 per million population per year [1,4-6]. Most cases are sporadic, while some are inherited due to genetic mutations (MEN-1, Li-Fraumeni, Beckwith-Wiedemann syndrome, Lynch syndrome) [7].

Most ACCs are functional, and present with symptoms of steroid hormone excess [2]. The most commonly secreted hormone is cortisol, resulting in Cushing syndrome (CS). In patients with ACC, the clinical symptoms tend to develop rapidly, usually over 3-6 months [4]. Diagnosing CS can be difficult due to its wide range of manifestations, including dermatologic (acne, facial plethora/flushing, thin skin, easy bruising, purple striae over the abdomen, and hirsutism), musculo-skeletal (proximal muscle weakness and atrophy, and osteoporosis), psychiatric (psychosis, panic disorder, depression, and irritability), immunological (susceptibility to infection, neutrophilia, and eosinophilia), and metabolic or endocrine (weight gain, fat redistribution with buffalo hump and moon face, hypertension, glucose intolerance, dyslipidemia, electrolyte imbalances, amenorrhea in women, and decreased libido in both genders) [8].

Our patient had a recent history of hypertension, diabetes mellitus, and weight loss within months prior to admission. The usual weight gain seen in patients with CS is commonly replaced by weight loss in ACC [9]. She presented with acute onset and recurrent episodes of psychosis, panic attacks, paroxysmal hypertension, tachycardia, flushing, and sweating. After ruling out substance use, differential diagnoses included panic disorder.
(PD) and PCC. A full laboratory evaluation was warranted to exclude PCC. The diagnosis of PCC is based on the serum and urine metanephrines, and imaging of the adrenal glands [10].

During our literature review, we tried to identify cases of CS that presented with paroxysms of hyperadrenergic symptoms. Reports of adrenal tumors combining features of CS and PCC are available, the most common being ACTH producing PCC, which is a rare cause of ectopic ACTH syndromes (3%) [11], and numerous cases have been reported [12-16]. However, such cases have elevated serum/urinary metanephrines, normetanephrines, and elevated serum ACTH levels, which was not the case in our patient; therefore, PCC was ruled out, and the patient was diagnosed with CS secondary to ACC. The most likely differential diagnosis for the clinical presentation in this patient with CS was panic attacks. Indeed, panic disorder is one of the most common psychiatric manifestations of CS (53%) [17]. It is characterized by the presence of recurrent episodes of panic attacks, defined by an abrupt surge of intense fear of losing control, “going crazy”, or dying, associated with 4 or more symptoms or physical signs, which include sweating, shaking, chills or heat sensations, dizziness, light-headedness, palpitations, tachycardia, chest pain or discomfort, shortness of breath, feeling of choking, nausea or abdominal distress, chills or heat sensations, paresthesias, and derealization or depersonalization. As it is the case in our patient, panic attacks can occur as often as several times a day, and without prodromes [18]. Other reported psychiatric manifestations in CS include depression (55-81%), anxiety (12%), mania or hypomania (3-27%), psychosis (8%), and confusion (1%) [17].

Table 1. Summary of the laboratory findings. Note that the increased renin level and the appropriately suppressed aldosterone level in the setting of excessive cortisol is suggestive of angiotensin-converting enzyme inhibitors (ACEI), used by our patient for hypertension treatment.

| Results (reference range) | 
|---------------------------|
| **Complete blood count** | Hemoglobin 15.0 (12.0-16.0 g/dL)  
Platelets 333 (150-450×10^3/mCL)  
White blood cells 11.71 (4.80-10.80×10^3/mCL)  
Neutrophils 80.7 (44.0-70.0%)  
Lymphocytes 12.0 (20.0-45.0%)  
Monocytes 6.1 (2.0-10.0%)  
Eosinophils 0.0 (1.0-4.0%)  
Basophils 0.3 (0.2-1.8%) |
| **Basic metabolic panel** | Sodium 147 mmol/L (136-145 mmol/L)  
Potassium 2.7 mmol/L (3.5-5.1 mmol/L)  
Chloride 99 mmol/L (98-107 mmol/L)  
Calcium 10.4 mg/dL (8.4-10.5 mg/dL)  
Bicarbonates 33 mmol/L (22-29 mmol/L)  
Glucose 260 mg/dL (74-109 mg/dL)  
BUN 17.0 mg/dL (6.0-23.0 mg/dL)  
Creatinine 0.59 mg/dL (0.50-0.90 mg/dL) |
| **Urine electrolytes (random)** | Sodium 47 mmol/L  
Potassium 25 mmol/L (20 mmol/L)  
Chloride 35 mmol/L |
| **Diabetes mellitus testing** | HbA1c 8.1 (4.0-5.6%) |
| **Thyroid function tests** | TSH 1.41 (0.27-4.20 uIU/mL) |
| **Adrenal function tests** | Serum aldosterone <3.0 (<23.2 ng/dL)  
Renin activity 3.651 (0.167-5.380 ng/mL/hr)  
Serum Normetanephrine 48.8 (0.0-244 pg/mL)  
Serum metanephrine 27.6 (0.0-88.0 pg/mL)  
24-hour urinary metanephrine 112 (36-209 mcg/24h)  
24-hour urinary normetanephrine 362 (131-612 mcg/24h)  
24-hour urinary cortisol 735 (3.5-45 mcg/24h)  
Morning serum cortisol 37.9 mcg/dL (6.0-18.4 mcg/dL)  
Morning serum cortisol after 1mg DXM: 30 mcg/dL (6.0-18.4 mcg/dL)  
ACTH < 1.5 ug/dL (7.2-63.3 mcg/dL) |

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Similar to our case, there are a few reports of CS presenting with acute psychosis in the literature [19,20].

**Conclusions**

Adrenal tumors can have overlapping symptoms. It is essential to recognize psychiatric presentations of cortisol-producing ACC to achieve early diagnosis and prevent mortality and morbidity. A full diagnostic workup is warranted to rule out differential diagnoses for adrenal masses, with a combination of hormonal levels, imaging, and histology. ACC is a very aggressive malignancy and the overall prognosis is poor. However, some studies have shown improved survival in patients with early diagnosis and curative resections.

**Declaration of Figures’ Authenticity**

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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**Figure 2.** Computed tomography (CT) abdomen with adrenal protocol showing a 45×37×46 mm mass in the right adrenal gland (see blue star), measuring 38 Hounsfield units (Hu) on precontrast imaging, 68 Hu at 90-s delay, and 98 Hu at 10-min delay. The mass contained several calcifications (see red arrow), suggesting degeneration or necrosis.