Cortisol-Producing Adrenocortical Carcinoma Presenting with Hypertensive Emergency

EF 1 Mitchell McGowan
E 2 Thomas Kalinoski

Corresponding Author: Thomas Kalinoski, e-mail: kali0136@umn.edu
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Patient: Female, 57-year-old
Final Diagnosis: Adrenocortical carcinoma • Cushing’s syndrome • hypertensive emergency
Symptoms: Anxiety • fatigue • generalized weakness
Clinical Procedure: Liver biopsy
Specialty: Cardiology • Critical Care Medicine • Endocrinology and Metabolic

Objective: Rare disease
Background: Hypertensive crisis is a relatively common condition often due to uncontrolled essential hypertension, but also potentially driven by one of many possible secondary etiologies. In this report, we detail a case of new-onset resistant hypertension leading to hypertensive emergency complicated by myocardial infarction and congestive heart failure secondary to underlying cortisol-producing metastatic adrenocortical carcinoma.

Case Report: A 57-year-old woman with no past medical history presented with generalized weakness and weight gain. Her blood pressure was 239/141 with a pulse of 117. Other vital signs were normal. A physical exam was notable for obesity and lower-extremity edema. Initial serum investigations were notable for leukocytosis, hypokalemia, metabolic alkalosis, and elevated troponin and BNP. An ECG showed anterolateral ST depression and left ventricular hypertrophy. A coronary angiogram revealed no coronary artery disease. Her ejection fraction was 25% by echocardiogram. Further investigation revealed severely elevated serum cortisol levels. CT scans were notable for left adrenal mass with evidence of hepatic, lung, and bone metastasis. A liver biopsy confirmed metastatic adrenocortical carcinoma. The patient was started on antihypertensives and a steroidogenesis inhibitor, with improvement in her blood pressure. She received palliative chemotherapy but later elected to pursue hospice care.

Conclusions: This report highlights the potential for underlying cortisol excess and adrenocortical carcinoma as a potential secondary etiology of resistant hypertension and hypertensive crisis. Due to the aggressive nature of this tumor, as demonstrated in this patient, a high index of suspicion and prompt attention are required for patients presenting with these clinical manifestations.

Keywords: Adrenocortical Carcinoma • Cushing Syndrome • Hypertension Resistant to Conventional Therapy • Hypertension, Malignant

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Background

Hypertension is a leading risk factor for death and disability-adjusted life years, and uncontrolled disease is related to an increased risk of cardiovascular and renal disease and stroke [1,2]. Hypertensive crisis is defined as a sudden elevation in blood pressure exceeding 180 mmHg systolic or 120 mmHg diastolic, and if there is any evidence of end-organ injury it is termed a “hypertensive emergency” [3,4]. Hypertensive emergency occurs in 1-2% of those diagnosed with hypertension, and the most common complications are stroke and acute heart failure. Initial treatment of hypertensive crisis involves slowly reducing blood pressure and treating comorbidities [4].

The diagnostic work-up of hypertensive crisis typically starts with a thorough medical history and physical examination, including measurement of all vital signs, an inspection of the cardiovascular and nervous systems, and an assessment of end-organ damage [4]. Further evaluation may include laboratory tests such as complete blood count, electrolytes, creatinine, blood gas, troponin, B-type natriuretic peptide (BNP), urinalysis, electrocardiogram (EKG), and imaging studies such as chest X-ray, echocardiography, computed tomography (CT) scan, and magnetic resonance imaging (MRI) [5]. Further tests are often performed to evaluate for causes of secondary hypertension, such as renal artery ultrasound for renal artery stenosis, a sleep study for obstructive sleep apnea (OSA), thyroid function tests for hypo- and hyperthyroidism, metanephrines for pheochromocytoma, and plasma aldosterone concentration and renin activity ratio for primary aldosteronism [6].

Another important consideration in the evaluation of secondary hypertension is hypercortisolism, or Cushing’s syndrome. While accounting for less than 1 in 1000 cases of secondary hypertension, this syndrome may be suspected when other characteristic physical exam findings exist in the patient, such as weight gain, hyperglycemia, and a rounded face (also known as “moon facies”). There are several causes of Cushing syndrome, the most common being iatrogenic, or corticosteroids used for medical treatment. Other etiologies include adrenal gland and pituitary tumors [7]. Adrenal gland tumors account for 18% of adrenocorticotropin-releasing hormone-independent cases and can be either benign or malignant [8]. Laboratory evaluation includes a complete blood count, metabolic panel, dexamethasone suppression test (DST), salivary cortisol or urinary free cortisol, serum adrenocorticotropic hormone (ACTH), and potential adrenal or pituitary imaging [7].

Adrenal gland tumors are very common, affecting 3-10% of the human population. Adrenocortical carcinoma (ACC), by contrast, is very rare with an incidence rate of 0.7-2.0 per million population per year [9,10]. Despite the low incidence, ACCs can cause significant morbidity and mortality due to their tendency to invade surrounding tissues, produce hormones, and spread to distant organs [10]. This cancer appears to have a bimodal age distribution, with its first peak before age 5 years and its second peak in the fourth and fifth decades of life [11]. No clear pathogenesis has been elucidated, but mutations in the protein TP53 have shown to be associated [12]. Increased incidence is also correlated with other well-known cancer-promoting conditions such as Li-Fraumeni, Beckwith-Weidemann, and multiple endocrine neoplasia type 1 [12-14].

ACC is classified into 2 main types based on the production of hormones: functional and nonfunctional. Clinical manifestations of ACC are typically due to the tumor’s ability to produce hormonal secretory products, including glucocorticoids and androgens. Approximately 60% of ACCs make these secretory products, with Cushing’s syndrome being the most common resulting condition [15]. The literature is currently lacking data on how often ACCs are discovered as a cause of secondary hypertension, but it is assumed to be relatively rare.

This case report illustrates a 57-year-old woman presenting with hypertensive emergency resulting from Cushing’s syndrome with an underlying functional adrenocortical carcinoma.

Case Report

A 57-year-old woman with no past medical history presented with 2 weeks of progressive generalized weakness and weight gain. She also endorsed recent-onset palpitations, lightheadedness, fatigue, abdominal and lower-extremity swelling, hand tremors, anxiety, paresthesias, and facial hair. She denied any chest pain or shortness of breath. The rest of the review of systems was unremarkable. There was no family history of malignancy, endocrine conditions, or heart disease. She did not use alcohol, tobacco, or other substances. She was not on any medications prior to presentation.

On presentation, her blood pressure was 239/141 mmHg with a pulse of 117 beats per minute. Her respiratory rate was 20 breaths per minute, pulse oximetry was 96% on room air, and body temperature was 36.9°C. The physical exam was remarkable for an anxious affect, obesity (body mass index of 46), moon facies, bilateral rales in the lower lungs, and 2+ pitting lower-extremity edema. Of note, no enlarged supraclavicular fat pads, facial hair, muscle atrophy, or ecchymosis were directly observed, and jugular venous pressure was not able to be assessed due to body habitus. The initial serum studies were remarkable for a white blood cell count of 15,900/µL with 82% neutrophils, platelets 358,000/µL, and hemoglobin 16.7 g/dL. Testing revealed sodium 140 meq/L, potassium 2.6 meq/L, chloride 91 meq/L, bicarbonate 33 meq/L, blood urea nitrogen 18 mg/dL, creatinine 0.84 mg/dL, glucose 119 mg/dL,
total calcium 9.8 mg/dL, magnesium 2.4 mg/dL, total bilirubin 0.5 mg/dL, alkaline phosphatase 122 u/L, aspartate aminotransferase 49 u/L, alanine aminotransferase 112 u/L, albumin 3.2 g/dL, and a c-reactive protein 0.10 mg/dL. Troponin was 0.44 ng/mL and brain natriuretic peptide (BNP) was 843 ng/L. Serum creatinine kinase was 70 u/L. Serum lactate dehydrogenase testing was not ordered. Venous blood gas revealed a pH of 7.60 and pCO2 of 44 mmHg. An EKG revealed evidence of anterolateral ST depression and left ventricular hypertrophy. A chest X-ray was within normal limits.

The patient was admitted with a diagnosis of hypertensive emergency with end-organ damage of myocardial infarction and new-onset acute decompensated heart failure, given the compilation of clinical signs and symptoms, ECG findings, and elevated troponin and BNP levels. She was given acute coronary syndrome treatment and antihypertensives. A coronary angiogram was performed, with no evidence of coronary artery disease. A coronary angiogram was performed, with no evidence of coronary artery disease. An echocardiogram revealed an ejection fraction of 25-30%, moderate left ventricular hypertrophy, and no regional wall motion abnormalities. A resistant hypertension work-up was initiated, revealing a thyroid-stimulating hormone (TSH) of 0.17 mIU/L (normal range 0.4-4.0 mIU/L) and free T4 of 0.80 ng/dL (normal range 0.9-1.7 ng/dL). Spot serum metanephrine was 0.22 nmol/L (normal range <0.5 nmol/L), and normetanephrine 0.28 nmol/L (normal range <0.9 nmol/L). Morning 08:00 serum cortisol was 43 µg/dL (normal range 26-200 µg/dL). Renal artery ultrasound did not reveal any evidence of renal artery stenosis. CT with intravenous contrast of the chest, abdomen, and pelvis revealed an 8.5 cm left adrenal mass, a T12 level spinal destructive lesion (Figure 1), numerous hypodense hepatic lesions (Figure 2), and pulmonary nodules (Figure 3). Liver biopsy pathology revealed abnormal epithelioid neoplastic cells staining positive for inhibin and Melan-A suggestive of metastatic adrenocortical carcinoma. No genetic work-up was performed.

The final diagnosis reached by Cardiology was hypertensive cardiomyopathy and type II non-ST elevation myocardial infarction due to hypertensive emergency. The patient was started on lisinopril, furosemide, spironolactone, carvedilol, and hydralazine, with overall stabilization in her blood pressure.

**Figure 1.** Contrast-enhanced CT imaging of the abdomen and pelvis revealing a left-sided adrenal mass (right arrow) and T12 level spinal destructive lesion (left arrow).

**Figure 2.** Contrast-enhanced CT imaging of the abdomen and pelvis revealing multiple hepatic lesions (arrows).

**Figure 3.** Contrast-enhanced computerized tomography angiography (CTA) of the chest revealing one of several pulmonary nodules (arrow).
addition, Endocrinology recommended oral ketoconazole, then later ololodrostat and mitotane for cortisol suppression. The patient was later seen by Oncology and was started on palliative chemotherapy with etoposide, doxorubicin, and cisplatin (EDP) and pembrolizumab. Her malignancy and Cushing’s symptoms (most notably proximal muscle weakness) progressed rapidly over several months and she elected to pursue hospice care.

Discussion

The case presented brings attention to a rare but life-threatening cause of hypertensive emergency with a couple of learning points. The first learning point is to be aware of the possibility of Cushing’s syndrome as a potential etiology of secondary hypertension and hypertension emergency and the clinical features that may prompt a further evaluation for this. The second learning point is to be vigilant about the potential for a malignant tumor to be the underlying etiology, necessitating a time-sensitive evaluation.

Initial investigation of hypertension serves to identify secondary causes and other comorbid conditions, and includes electrolytes, glucose, urinalysis, complete blood count, and lipid panel. Further evaluation of secondary etiologies should be pursued if hypertension is diagnosed before age 30, there is an abrupt onset, a patient is not responsive to 3 medications (including a diuretic), in the case of severe hypertension with end-organ damage, and if there is associated hypokalemia or metabolic alkalosis [16]. Our patient fit most of these criteria, with an abrupt onset, resistance to lisinopril, furosemide, spironolactone, and carvedilol, hypokalemia and metabolic alkalosis, and presentation with hypertensive emergency.

The prevalence of endogenous Cushing’s syndrome is very low, at about 1 case per million population, but most of those people will be diagnosed with hypertension. Due to the multiple organ systems involved, the presentation of typical Cushing’s syndrome is variable. The most common clinical feature of the disease is obesity and weight gain, with a prevalence of 70-95%. Other highly prevalent symptoms include menstrual irregularity (70-80%), neuropsychiatric symptoms (70-85%), moon facies (81-90%), and muscle weakness (60-82%) [17]. The wide variety of presenting symptoms makes diagnosis of Cushing’s syndrome elusive and probably underdiagnosed. The patholgy of hypertension in Cushing’s syndrome can be multifactorial; therefore, it is important to obtain a thorough history and physical exam and to consider additional contributing etiologies such as obesity, OSA, and anxiety.

Similarity, our patient presented with generalized weakness and weight gain, which are vague symptoms by themselves and are often explained by more common conditions such as depression, medication adverse effects, and hypothyroidism. Interestingly, our patient did not have ecchymosis, supravclavicular fat pads, or objective hirsutism, which are typically found [7]. The diagnosis of Cushing’s syndrome was made only after further investigation of patient history, a complete and thorough physical exam, and laboratory work-up.

The most significant finding on initial laboratory results was the hypokalemia measured at 2.6 meq/L and the metabolic alkalosis with a pH of 7.60 and bicarbonate of 33 meq/L. Cushing’s syndrome has been well-known to cause hypokalemia via excess cortisol binding to mineralocorticoid receptors with increased sodium and water retention and potassium and hydrogen ion excretion. Metabolic alkalosis in Cushing’s syndrome is expected, also due to mineralocorticoid receptor activation [18]. Of note, although this patient’s aldosterone level was appropriately suppressed, the renin level was uncharacteristically elevated [19]. As this laboratory study was obtained after initiation of furosemide for congestive heart failure, we suspect that the medication influenced the result [20]. Another non-specific sign of Cushing’s syndrome for our patient was a leukocytosis of 15 900/µL with 82% neutrophils. A high cortisol state has been known to cause leukocytosis via several mechanisms, including increased release of polymorphonuclear cells into the circulation, delayed apoptosis, and inhibiting neutrophil adhesion molecules [21]. Morning and evening cortisol testing was completed as the initial screening test for Cushing’s syndrome and were markedly abnormal. Once the initial screening tests were positive, current guidelines state that further work-up is needed to distinguish an ACTH-dependent or -independent process [7]. Serum ACTH was undetectable, which identified an ACTH-independent source of cortisol excess. Therefore, a CT of the abdomen and pelvis was performed, revealing multiple masses, and further biopsy revealed ACC.

ACC typically presents either due to effects of hormone excess or tumor growth, and the diagnosis is typically made during the investigation of these symptoms [11]. Our patient presented acutely over 2 weeks with mainly hormonal symptoms, suggesting an aggressive tumor with a rapid rise in serum cortisol. She did not experience clear symptoms due to tumor bulk or metastasis. Constitutional symptoms were likely obscured by the symptoms from her Cushing’s syndrome. Unfortunately, the prognosis of advanced ACC is poor, with a 5-year survival rate estimated to be 10-25% [9]. With the rapid disease progression over months despite palliative chemotherapy, our patient soon transitioned to hospice care.

Conclusions

This report emphasizes the uncommon condition of Cushing’s syndrome as a secondary etiology of resistant hypertension
and hypertensive crisis, and the potential for underlying malignancy as a driver for it. Early recognition and evaluation for these clinical manifestations is essential, as the aggressive nature of adrenocortical carcinoma requires timely treatment.

References:


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