
CLINICAL CASE OF THE MONTH

New Onset Hypertension and Diabetes in a 24 Year-Old Man

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INTRODUCTION

Pituitary adenomas are classified based on size (macroadenomas > 1 cm), immunohistochemistry, electron microscopy, and hormone functional status. Overall, pituitary adenomas (including micro and macroadenomas) have a prevalence of 16.7%, making them a relatively common pathological finding. Pituitary macroadenomas are even less common, with a prevalence of 0.2%. Furthermore, ACTH secreting tumors are found in only 4.9% of patients with pituitary adenomas.¹ An ACTH secreting pituitary adenoma results in Cushing's disease, which is a hypersecretion of ACTH from the adenoma itself. In general, this hypersecretion leads to a cushingoid appearance, which is characterized by central obesity, moon facies, proximal muscle weakness, easy bruising, striae, hirsutism, and an increased dorsocervical fat pad. It is often found in conjunction with glucose intolerance, polyuria, polydipsia, hypertension, hypokalemia, metabolic alkalosis, and renal calculi.² Cushing's disease is the leading cause of ACTH dependent Cushing's syndrome, occurring in 65-70% of patients.³ Early diagnosis and treatment of this curable disease can significantly decrease morbidity and mortality of these patients; therefore, despite its rare occurrence, it should remain a differential diagnosis for patients presenting with the aforementioned symptoms.

CASE PRESENTATION

A 24 year-old man with a past medical history of asthma and sickle cell trait presented to the emergency department (ED) with complaints of polyuria, polydipsia, dry mouth, and blurry vision for two weeks. He complained of a white adherent material on the roof of his hard palate. Additionally, he described a three year history of 30 pound weight gain despite not changing his diet or lifestyle. He also endorsed generalized abdominal pain and malaise. He was noted to have an elevated blood pressure of 172/111 mmHg, as well as an elevated blood glucose of 565 mg/dL and a BMI of 36.5 kg/m². In the ED, the patient was diagnosed with new onset diabetes mellitus. He was given intravenous fluids, a prescription for metformin, a blood glucometer, diabetic diet education, and a follow-up visit with a primary care provider.

The day prior to his follow-up, he was involved in a motor vehicle accident. He was ambulatory at the scene with no loss of consciousness. He was brought to the ED by EMS, where he continued to endorse all complaints from his prior ED visit, with additional complaints of midline neck pain and intensified generalized abdominal pain. His past family history was relevant for a father with sickle cell disease and a grandfather with type 2 diabetes mellitus and hypertension. He denied any past surgeries, use of illicit substances, or use of alcohol. He was a current every-day smoker with a three pack-year history. His only medication was his recently prescribed metformin, and he denied any allergies. His vitals at presentation were: blood pressure 170/108 mmHg, pulse 88/min, respiratory rate 22/min, temperature 99.2°F, and BMI 37.6 kg/m². Physical examination revealed moon facies (Image 1), an increased dorsocervical fat pad (Image 2), and oropharyngeal candidiasis. The patient was noted to be tender to palpation in the left upper quadrant, with diffuse abdominal striae and central obesity (Image 3). The patient also had striae over both upper extremities, pretibial edema bilaterally, onychomycosis, and tinea pedis bilaterally.

Laboratories revealed a glucose of 855 mg/dL [69-99 mg/dL], potassium of 2.7 Mmol/L [3.6-5.2 Mmol/L], hemoglobin A1c of 14.2%, triglycerides of 493 mg/dL [<150 mg/dL], and a metabolic alkalosis. In the ED, a computed tomography (CT) scan of the cervical spine was unremarkable. A CT scan of the abdomen and pelvis demonstrated bilateral avascular necrosis of his femoral heads as well as bilateral adrenal hyperplasia. The patient was then admitted for further evaluation and management. A random cortisol level was > 60 mcg/dL [3-16 mcg/dL]. The patient was started on long acting insulin in addition to sliding scale insulin for his hyperglycemia, and losartan for his elevated blood pressure. Endocrinology was consulted and additional lab tests were ordered. A 24-hour urine cortisol returned at 9205 mcg/dL [< 50 mcg/dL], an ACTH level returned at 245 mcg/dL [3-60 mcg/dL], and a 24 hour urine 5-HIAA level was within normal limits. In addition, a low dose dexamethasone suppression test was performed, which failed to correct the patient's cortisol, the level returning at 55 mcg/dL.

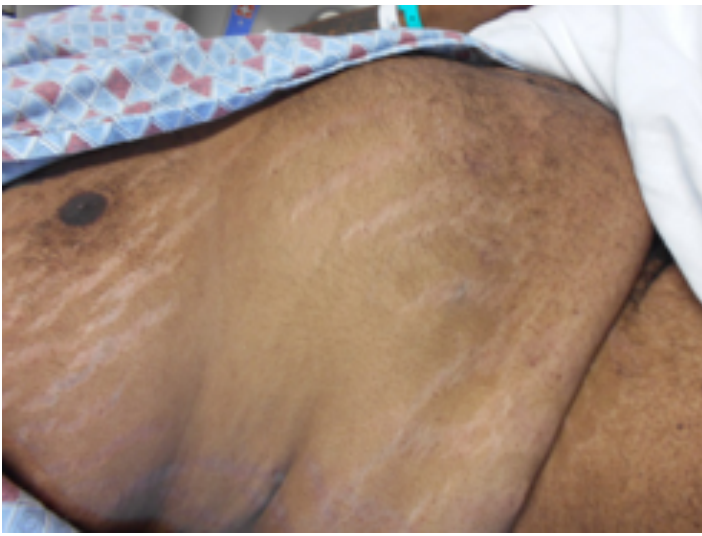
Image 1



Image 2



Image 3



The above images display typical features of Cushing's syndrome as seen in our patient, including moon faces (Image 1), increased dorsocervical fat pad (Image 2), and abdominal striae and central obesity (Image 3).

Upon further questioning, the patient mentioned early morning headaches which typically resolved after sitting or standing for several hours. A magnetic resonance imaging (MRI) of the brain with dynamic pituitary imaging was performed in light of this history coupled with the patient's laboratory abnormalities and a high suspicion for Cushing's disease. The MRI demonstrated a macroadenoma of the pituitary measuring 8mm x 19mm x 8mm, eroding the sella as well as invading into the sphenoid sinus. The patient was diagnosed with Cushing's disease, and Neurosurgery was consulted. The patient underwent successful endoscopic transsphenoidal resection of the macroadenoma, which was felt to be complete. Pathology demonstrated a monomorphic population of mononuclear cells compatible with a pituitary adenoma. The patient was doing very well when seen post-operatively by the neurosurgery service.

DISCUSSION

While our patient did have a classic presentation of Cushing's disease, without a high level of suspicion he may have gone undiagnosed for quite some time and instead started on traditional management for hypertension and diabetes. In order to diagnose Cushing's disease, it is important to first diagnose Cushing's syndrome and then look for the underlying cause. The Endocrine Society advises against widespread testing for Cushing's syndrome, rather testing when there is a high level of suspicion, such as patients with unusual features for age (hypertension and osteoporosis, as seen in our patient), children with decreasing height percentile and increasing weight, patients with progressive features predictive of Cushing's syndrome, and patients with an adrenal incidentaloma.⁴ First, exogenous glucocorticoid exposure must be excluded by obtaining a thorough drug history including skin creams, herbal medications, joint injections, and megestrol acetate. Then, for initial testing, the Society recommends one of the following first line tests: 24-hour urinary free cortisol, late night salivary cortisol, or low dose (1mg) dexamethasone suppression test.⁴ Abnormal results include high cortisol levels with loss of the expected diurnal pattern of cortisol secretion and failure of normal feedback inhibition. If testing reveals abnormal results, physiologic causes of hypercortisolism (including obesity, pregnancy, psychologic stress, poorly controlled diabetes, and chronic alcoholism) should be excluded, and an endocrinologist should be consulted. Confirmation of abnormal cortisol levels should be made by repeating the same test initially found to be abnormal.⁴

Once an elevated cortisol level is confirmed, the next step is to determine if the cause is ACTH-dependent or ACTH-independent by measuring the plasma ACTH level. If the ACTH level is <5pg/mL, an ACTH-independent cause should be suspected, such as adrenal adenomas or carcinomas, as well as adrenal hyperplasia. At this point, adrenal imaging should be performed. On the other hand, ACTH is elevated (>20pg/mL), as with our patient, an ACTH-dependent cause of Cushing's syndrome is suggested. A pituitary MRI is then performed to look for the source of ACTH secretion, as pituitary adenomas are the most common source

of ACTH dependent Cushing's syndrome.⁵ If a microadenoma (<1cm) or macroadenoma (>1cm) is identified, Inferior Petrosal Sinus Sampling (IPSS) should be performed, which is the gold standard for diagnosis. An IPSS combined with pre- and post-CRH stimulation samples detects Cushing's disease with 95% sensitivity and 93% specificity. If the pre-CRH central to peripheral ACTH ratio is > 1.7 and a post-CRH central to peripheral ACTH ratio is >3.3, a pituitary source can be confirmed as the site of excess ACTH production, making a final diagnosis of Cushing's disease.⁶ If these ACTH ratio requirements are not met, an ectopic source of ACTH secretion is suspected and must be investigated further, most commonly focusing on lung malignancies.

The overall goals of treatment for Cushing's disease are reversal of clinical signs and symptoms, normalization of endocrine labs, and prevention of recurrence. The definitive treatment for Cushing's disease is a transsphenoidal adenomectomy. This surgical approach is most successful when the patient has a microadenoma that is well circumscribed and not intertwined in normal pituitary tissue. If the adenoma is not well circumscribed, a subtotal hypophysectomy may be performed; yet, this procedure is associated with greater risk of post-surgical pituitary dysfunction and is not as desirable for patients interested in future fertility. It is also associated with only a 70% remission rate compared to up to 90% with selective adenomectomy.⁷ If the adenoma is unable to be resected or if the patient is interested in future fertility, pituitary irradiation may be used as first line treatment for Cushing's disease (but is often used as second line treatment when surgery fails). If no surgical treatment is possible, Cushing's disease can be managed medically, although this is sub-optimal. Drug classes such as adrenal enzyme inhibitor and adrenolytic agents (ketoconazole, metyrapone, etomidate, mitotane, and mifepristone), pituitary-directed drugs (cabergoline), and somatostatin analogs (pasireotide) are the most commonly used medical therapies. Unfortunately, toxicities due to side effects of these medications often limit their use.⁸

A patient is considered to be in remission if the morning cortisol level is <5ug/dL within 7 days after surgery. Remission rates are lower for macroadenomas (~48%) compared to microadenomas (~76%). After surgery, patients require glucocorticoid replacement until the HPA axis recovers, typically within one year. However, early recovery of the HPA axis may indicate a higher risk for recurrence in the future. Late-night serum or salivary cortisol levels should be monitored, starting at the time of HPA axis recovery, as an elevated value is the earliest detectable sign of recurrence. It is also important that patients with Cushing's syndrome receive long term follow up for the associated comorbidities, including obesity, hypertension, cardiovascular risk, and osteoporosis, which may never completely resolve. They require follow up for recurrence throughout the remainder of their life.⁸

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