Diagnosis of Cushing Syndrome during an Infertility Evaluation

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Abstract

Many cases of Cushing's disease or syndrome are diagnosed after progression of initial non-specific symptoms including weight gain, hirsutism, mood changes and hypertension. In this unusual case, abnormality of the cortisol axis was considered after finding a low level of the adrenal androgen precursor, dehydroepiandrosterone sulfate, during an infertility evaluation for anovulation. Low dehydroepiandrosterone sulfate proved secondary to decreased pituitary adrenocorticotropin hormone production from hypercortisolism associated with an adrenal adenoma. Although dehydroepiandrosterone sulfate levels naturally decline with aging, abnormally low levels should raise suspicion for Cushing's syndrome.

Keywords: Cushing's syndrome; Infertility; Ovulatory dysfunction; Amenorrhea; Dehydroepiandrosterone sulfate

Introduction

Given the low incidence of Cushing's disease and syndrome of 0.7 to 2.4 per million per year and the often non-specific and common symptoms of weight gain, menstrual abnormalities, hypertension, lethargy and mood disorders, this diagnosis is rarely initially considered. Many cases are not diagnosed until symptoms have progressed in severity such as muscle weakness with wasting of the limbs, facial rounding, frontal balding, osteoporosis, diabetes and easy bruising. The case described herein shows a very unusual situation where an abnormality of the Hypothalamic-Pituitary-Adrenal (HPA) axis was considered due to a low level of the adrenal androgen precursor, Dehydroepiandrosterone Sulfate (DHEAS). This level was drawn for evaluation of infertility with an ovulation. This abnormal laboratory value leads to the diagnosis of Cushing's syndrome secondary to an adrenal adenoma.

Case Presentation

A 41 year old G0 female with primary infertility revealed a history of irregular menses with subsequent amenorrhea for the last 4 months. She denied any vasomotor symptoms, galactorrhea or pelvic pain. She had not previously received fertility evaluation or treatment. Past medical history revealed no prescription drugs and no significant illnesses or surgeries. Social history and family history were unremarkable. Review of systems was pertinent for inability to lose weight, occasional irritable bowel syndrome with diarrhea, menstrual migraine history and long-term history of dysthymia without current medical treatment. Physical examination showed blood pressure of 162 systolic, 108 diastolic, body mass index of 28.19 kg/m^{2} and otherwise non-contributory. Laboratory testing showed anti-mullerian hormone 0.53 pmol/L (0.074 ng/mL), follicle stimulating hormone 8.7 IU/L, estradiol 168.88 pmol/L (46 pg/mL), thyroid stimulating hormone 2.44 mIU/L, prolactin 12.89 μg/L, DHEAS 0.081 μmol/L (3 μg/dL; normal 35-430) and total testosterone <0.24 nmol/l (7 ng/dL). Due to very low androgen and androgen precursor levels, additional testing of the pituitary-adrenal axis was performed including morning ACTH 0.44 pmol/L (2 pg/mL; normal 15-66), cortisol 361.38 nmol/L (13.1 μg/dL; normal 5-25), late afternoon cortisol 361.38 nmol/L (13.1 μg/dL) and 24 h urinary free cortisol 193.2 nmol/d (70 μg/24 hr; normal 3.5-45). A 1 mg overnight dexamethasone suppression test failed suppression with a cortisol level of 300.69 nmol/L (10.9 μg/dL). A non-contrast CT of the abdomen showed a 3.9 cm × 2.6 cm mass of the left adrenal (Figure 1A). A left adrenalectomy was performed with pathology showing an adrenal cortical adenoma (Figure 1B). Follow-up laboratory testing showed normalization of cortisol levels.

Discussion

Cushing's syndrome, secondary to supraphysiologic levels of glucocorticoids, most commonly arises from ACTH producing pituitary tumors (Cushing's disease) 80% of the time or from direct secretion of cortisol from adrenal tumors 20% of the time [1]. The majority of adrenal tumors are unilateral with 80% benign and 20% malignant [2].

With an annual incidence of 0.2 to 5 per million people and a characteristic insidious onset of non-specific symptoms, evaluation for Cushing's is typically delayed [3-5]. Diagnosis can be particularly challenging in cases with mild hypercortisolism and a subtle clinical presentation. Weight gain is the most common symptom in Cushing's syndrome and evidence of protein wasting, such as proximal weakness, thin skin and easy bruising, can most reliably distinguish Cushing's syndrome from other causes of weight gain [6]. There is no single sign or symptom that is pathognomonic for Cushing's syndrome and clinical presentation is influenced by age, sex, severity and disease duration. The symptom complex includes hirsutism, acne, weight gain, hot flashes, hypertension, moon facies or buffalo hump, osteopenia, depression, emotional lability, menstrual abnormalities, decreased libido, glucose intolerance, dyslipidemia and decreased growth velocity in children [3,6]. Diagnosing and treating Cushing's syndrome is critical given a two to three-fold increased risk of mortality with higher rates of venous thromboembolism, myocardial infarction and stroke [5,7]. Appropriate screening tests for Cushing's include 24-h Urinary Free Cortisol (UFC), Late Night Salivary Cortisol (LNSC) and overnight Low-Dose (1 mg) Dexamethasone Suppression Test (LDDST). The UFC has an advantage of determining hypercortisolism irrespective of altered corticotropin-binding globulin levels as seen in pregnancy and with estrogen therapy. Disadvantages include inaccuracies from high fluid intake, incomplete urine collection and abnormal renal function [8]. LNSC detects loss of diurnal cortisol production seen in Cushing's syndrome, differentiating from pseudo-Cushing's syndrome, associated with depression, malnutrition or alcohol dependence. However, LNSC is not reliable with tobacco abuse, critical illness or disturbed sleep patterns [1]. A LDDST should normally suppress the morning cortisol to less than 50 nmol/liter (1.8 μg/dL). Due to loss of feedback inhibition on the HPA axis, an elevated cortisol level suggests Cushing's. The LDDST has decreased reliability in patients with malabsorption disorders, liver or kidney failure or patients taking medications that interfere with CYP3A4 metabolism [8].

With positive screening tests, a morning ACTH level is used to differentiate between ACTH-dependent and ACTH-independent causes. High ACTH suggesting a pituitary secreting adenoma or ectopic ACTH production requires brain MRI, while low ACTH suggesting an adrenal tumor requires an abdominal CT scan. Elevated ACTH without radiographic evidence of a pituitary adenoma requires additional testing. Noninvasive testing to help discriminate a pituitary source from ectopic source includes High Dose Dexamethasone Suppression Test (HDDST) and CRH (Corticotropin Releasing Hormone) stimulation. The former works on the principal that pituitary corticotroph lesions retain partial inhibition by high-dose glucocorticoids whereas ectopic tumors do not. Similarly, the CRH stimulation may help differentiate due to retained response in pituitary lesions, not seen in ectopic tumors. The gold-standard for diagnosis remains bilateral inferior petrosal sinus blood sampling. A
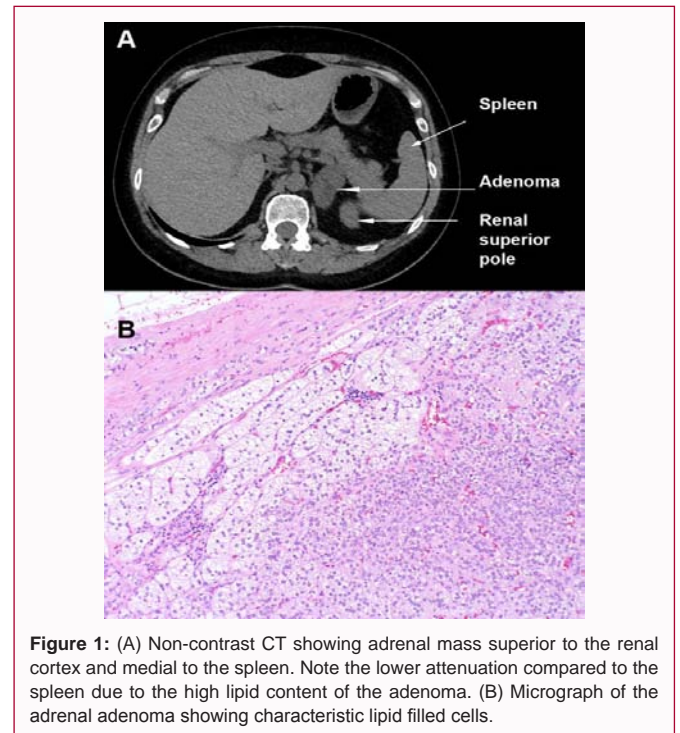

Figure 1: (A) Non-contrast CT showing adrenal mass superior to the renal cortex and medial to the spleen. Note the lower attenuation compared to the spleen due to the high lipid content of the adenoma. (B) Micrograph of the adrenal adenoma showing characteristic lipid filled cells.

central to peripheral ACTH ratio of 2:1 prior to CRH administration or 3:1 after CRH administration has a sensitivity of approximately 94% and a specificity >99% for a pituitary source [9].

In the case subject presenting with infertility, oligomenorrhea, inability to lose weight and dysthymia, more common diagnoses of polycystic ovarian syndrome, hypothyroidism, and hyperprolactinemia would be considered. In addition, obesity and dysthymia most commonly lack a secondary cause. The finding of a very low DHEAS level led to the suspicion of ACTH suppression with Cushing's syndrome resulting from an adrenal tumor. Although DHEAS is not a screening test for Cushing's, abnormal levels warrant further evaluation. In a study of 28 patients with Cushing's syndrome from an adrenocortical adenoma, 100% had abnormally low DHEAS levels. In contrast, 29% of 36 patients with Cushing's disease had abnormally high DHEAS levels [10].

Hypercortisolism contributes to infertility *via* ovulatory dysfunction. In 45 premenopausal women with Cushing's syndrome, 80% of patients had menstrual irregularities, 33% with amenorrhea and 31.1% with oligomenorrhea [11]. The primary mechanism is cortisol-induced inhibition of Gonadotropin-Releasing Hormone (GnRH) release from the hypothalamus and LH and FSH release from the pituitary [11]. At the level of the gonads excess glucocorticoids can inhibit sex steroid hormone production and cell apoptosis [12]. Examination of ovarian tissue in premenopausal patients with Cushing's syndrome has shown a trend towards reduced primordial follicles and fibrosis consistent with a mechanism of hypogonadotrophic hypogonadism [13]. Decreased libido with Cushing's syndrome may also contribute to infertility [14].

With ACTH-dependent Cushing's, adrenal androgen excess results in increased peripheral conversion to estrogens along with decreased hepatic production of Sex-Hormone Binding Globulin (SHBG) resulting in higher free estradiol levels, both yielding inappropriate feedback on the HPO axis [15,16].

Adrenocortical adenoma, seen in this patient, is the most common cause of ACTH-independent Cushing's [17].

These tumors average 3.5 cm in size with a direct correlation of size and malignancy, while size does not correlate with hormone levels. Approximately 73% of cells within the adenoma are lipid-rich yielding lower attenuation on unenhanced CT compared to the spleen. Similarly, Chemical Shift Imaging (CSI) on MRI shows a relative signal loss compared to the spleen due to the lipid content. CT and MRI are the best imaging modalities, typically with the former preferred. Benign adenomas are characteristically round or oval with smooth walls and homogeneous interior. In contrast, adenocarcinomas are irregular in shape with heterogeneous interior often due to hemorrhage [18]. In summary, this case of Cushing's syndrome found in a woman presenting for ovulatory dysfunction related infertility highlights the non-specific symptoms of the disorder along with the common finding of suppressed DHEAS. Very low DHEAS levels would be unusual in other causes of ovulatory dysfunction.

References

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