Journal of Women's Health Care

Lal and Basina, J Women's Health Care 2018, 7:1
DOI: 10.4172/2167-0420.1000e132

Editorial Open Access

Postmenopausal Hyperandrogenism

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Received date: January 29, 2018; **Accepted date:** February 05, 2018; **Published date:** February 12, 2018

Editorial

Hirsutism is a fairly common diagnosis affecting 10% of women [1]. Mild symptoms are not always brought to medical attention, but severe cases, especially in menopause that are associated with hyperandrogenism, require evaluation and treatment. We present a case of postmenopausal hirsutism to demonstrate the diagnostic and therapeutic challenges seen in practice. A 55 year-old postmenopausal woman with history of multi nodular goiter, autoimmune hepatitis, lupus erythematosus panniculitis, diabetes and acid reflux presents with restlessness, increased libido, hair loss, worsening hirsutism, and 25-pound weight loss over 2 months. Medications include azathioprine, metformin, lisinopril, and omeprazole. Physical examination revealed BMI of 34 kg/m^2, severe hirsutism (Ferriman-Gallwey score of 18), receding hairline, goiter, prior scarring from abdominal procedures and normal external genitalia without clitoromegaly. Labs included TSH 1.05 (normal 0.5-4.5), hemoglobin A1c of 6.1% (normal <5.7), LH 29.8 mIU/mL (normal 20-70), FSH 38.5 mIU/mL (normal 30-120), total testosterone 94.7 ng/dL (normal 7-40), free testosterone 2.2 ng/dL (normal <1), estradiol 28.5 pg/mL (normal <20), DHEA-S 25.2 µg/dL (normal 15-200), cortisol 7.1 µg/dL (normal 7-20) and ACTH 15 pg/mL (10-60 pg/mL). Screening tests for occult Cushing's syndrome and pheochromoctyoma were negative.

CT scan of the abdomen and pelvis demonstrated normal pelvic structures but revealed a 1 cm left adrenal adenoma (Figure 1) confirmed on adrenal MRI.

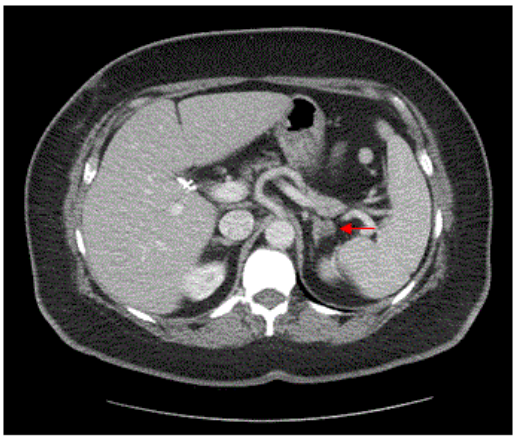

Figure 1: CT demonstrating left adrenal mass (arrow).

Transvaginal/Transabdominal ultrasound allowed only partial visualization of the left ovary. Due to the small size of adrenal nodule and peri-menopausal timing of the onset of the symptoms, ovarian pathology was suspected. Laparoscopic bilateral salpingo-oophorectomy was performed. It revealed grossly normal ovaries (Figure 2) but histology confirmed bilateral ovarian hyperthecosis. Testosterone normalized following surgery and symptoms resolved.

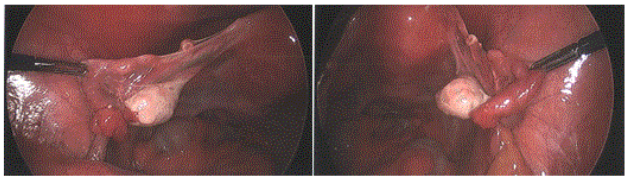

Figure 2: Laparoscopic view of normal-appearing bilateral ovaries.

Physiologic changes of normal menopause consist of progressive follicular atresia with decreased secretion of inhibin B, which inhibits FSH. The increased FSH concentration maintains ovarian production of estrogen preceding menopause. Testosterone production is preserved and some is converted to estrogen by aromatase. As a compensation for falling estrogen, Gonadotropin Releasing Hormone (GnRH) rises resulting in elevation of both LH and FSH. In early menopause the ovarian theca cells continue to produce androstenedione and testosterone. Adrenal androgen production is preserved throughout this process [2].

Additionally, sex hormone binding globulins are reduced increasing the free bioactive androgens [3]. The result is an overall increase in the ratio of androgens to estrogen that may result in mild hirsutism. Rapid progression to severe hirsutism, alopecia or acne is suggestive of pathology [4]. Benign hyperandrogenism is suspected when total testosterone measures of 40-140 ng/dL [4,5]. Insulin resistance and polycystic ovarian syndrome are the most common causes of female hyperandrogenism. Elevated insulin levels induce theca cells to produce androgens and act as a co-gonadotropin augmenting LH activity [6].

Hyperthecosis is another gonadotropin-dependent ovarian hyperandrogenism where in luteinized theca cells throughout the ovarian stroma over express testosterone [7]. Congenital adrenal hyperplasia involves enzyme deficiencies producing an ACTH-dependent adrenal hyperandrogenism due to shunting of steroid precursors to androgens [8]. ACTH excess from Cushing's disease stimulates adrenal androgen production. Another cause is accidental or intentional exposure to androgenic medications or supplements.

When virilization occurs with clitoromegaly, male-pattern baldness, and deepening of the voice, malignancy must be excluded [5]. A review of androgen-secreting adrenocortical tumors reported free testosterone >6.85 pg/mL had the best sensitivity (82%) and specificity

(97%) but there is clinical overlap [9]. Adrenal tumors are frequently gonadotropin-independent, although exceptions exist [10]. Ovarian malignancy also tends to be gonadotropin-independent, but basal hormone measures are not sufficient for diagnosis.

Few studies have explored the best method for evaluating postmenopausal hyperandrogenism [4,5]. Several others have reported postmenopausal hyperthecosis in the presence of adrenal incidentaloma. Our case is an example where algorithms would incorrectly suggest adrenal pathology. However, the prevalence of disease favors an ovarian over adrenal androgen source. GnRH agonist testing cannot differentiate adrenal and ovarian etiologies; dexamethasone suppression testing may help [10]. It is crucial for providers to differentiate between hormonal changes of normal aging and pathological cause of hyperandrogenism.

Acknowledgement

Dr. Lal is a Stephen Bechtel Endowed Endocrinology Fellow through the Stanford Child Health Research Institute and is supported by a Diabetes, Endocrinology and Metabolism Training Grant (T32 DK007217) from NIDDK.

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