Hilar Leydig Cell Tumor Presenting as Hirsutism in a 51-Year-Old Woman

Vinni Grover, MD
Ambika Babu, MD

Hirsutism is commonly defined as excessive terminal hair growth in a male-like pattern that occurs in females. Its reported incidence varies between 5% and 15% in the literature.[1–3] In many cases, hirsutism results from an increased androgen level, which accelerates the rate of hair growth and transforms fine vellus to coarse terminal hair in androgen-sensitive areas.[4] Although 80% of patients with hyperandrogenism experience hirsutism, not all patients who experience hirsutism have hyperandrogenism; these cases are considered idiopathic.[5] The most common causes of hirsutism are polycystic ovary syndrome (PCOS; 53%–82%)[5] and idiopathic hirsutism (5%–25%).[6] A minority of cases are caused by nonclassic congenital adrenal hyperplasia (1%–8%), congenital adrenal hyperplasia (< 1%), the hyperandrogenic insulin resistance acanthosis nigricans (HAIR-AN) syndrome (3%), Cushing's disease (0.4%), medication use (eg, exogenous testosterone, dehydroepiandrosterone [DHEA], androgenic progestins; 0.4%), and androgenic tumors (≤ 1%).[5–9] This article reviews the case of a 51-year-old woman who presented with worsening hirsutism, which was subsequently found to be caused by a hilar Leydig cell tumor.

CASE PRESENTATION

Initial Presentation and History

A 51-year-old gravida 2, para 2 African American woman was referred to an endocrinologist by her primary care physician for evaluation of worsening hirsutism. The patient stated that she had always been hairy but had noticed increasing growth and coarseness of hair on her arms, legs, chest, and abdomen over the last 4 years. The patient reported that 4 years ago she began shaving her face 2 times per week, which progressed to once daily for the past month. She denied experiencing voice changes, scalp hair loss, recent acne, recent weight changes, fatigue, and galactorrhea. In addition, the patient denied symptoms suggestive of menopause (eg, vaginal xerosis, vasomotor flashes) as well as changes in her extremities. She indicated that she had regular menses (age of menarche, 13 yr) until she underwent hysterectomy with ovarian conservation for uterine fibroids approximately 20 years ago. She had 2 living children. Her past medical history was significant for hypercholesteremia and gastroesophageal reflux disease, for which she was taking simvastatin and lansoprazole, respectively. The patient denied use of corticosteroids or sex steroids as well as over-the-counter or herbal medications. Social history was unremarkable. There was no family history of hirsutism, diabetes, or premature heart disease.

Physical Examination

On examination, the patient had a body mass index of 38 kg/m^2 and a blood pressure of 128/77 mm Hg. Other vital signs were within normal limits. Coarse terminal hair was present over the upper lip, chin, chest, lower abdomen, inner thighs, lower back, and sacral area. Her modified Ferriman-Gallwey score was 17 out of 36 points.[10] There was no moon facies, buffalo hump, acanthosis nigricans, skin changes, galactorrhea, thyromegaly, or striae. No abdominal or pelvic adnexal masses were palpated; however, clitoromegaly (3.2 × 1.1 cm) was present. The remainder of the physical examination was unremarkable.

Laboratory and Imaging Studies

Laboratory studies revealed a normal complete blood count and metabolic profile. Endocrinologic work-up revealed normal hormone levels except for increased levels of total and free testosterone (**Table**), which was more than 10 times the upper limit of normal. These findings suggested that excessive testosterone was responsible for the patient's hirsutism and clitoromegaly. The normal levels of DHEA sulfate

Dr. Grover is an internal medicine resident, John Stroger Hospital of Cook County, Chicago, IL. Dr. Babu is an attending physician, Division of Endocrinology, John Stroger Hospital of Cook County; and an assistant professor of medicine, Rush University Medical Center, Chicago, IL.

Table. Baseline Hormonal Work-up of the Case Patient

Hormone	Patient Values	Normal Values
Prolactin (ng/mL)	5.61	3–30
Thyroid-stimulating hormone (μIU/mL)	0.81	0.4–6.0
Free triiodothyronine (pg/mL)	3.38	2.3–4.2
Free thyroxine (ng/mL)	1.07	0.6–1.7
8 AM Cortisol level (μg/dL)	9.54	4–22
Female total testosterone (ng/dL)	592	3–46
Female free testosterone (pg/mL)	122	≤ 6.9
Dehydroepiandrosterone sulfate (ng/mL)	648	350–4300
Dehydroepiandrosterone (ng/dL)	277	130–980

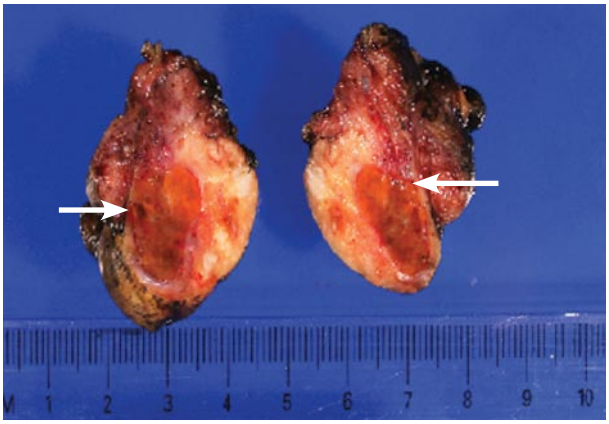

Figure 1. A photograph of the cut section of the patient's left ovary demonstrating a Leydig cell tumor measuring 1.5 × 1.5 × 1.2 cm in the hilar region (*arrows*).

(DHEA-S) argued against the adrenal glands as the source of excessive testosterone and implicated the ovaries as a possible source. A review of the patient's medical records confirmed that both ovaries were retained when she underwent hysterectomy. Subsequently, a computed tomography (CT) scan of the abdomen and pelvis was performed, which demonstrated normal adrenal glands and ovaries. The right ovary measured 2.5 × 1.5 cm, and the left ovary measured 2.5 × 2.2 cm. Pelvic ultrasonography was also normal.

Surgery

A gynecologic consultation was obtained, and the patient was admitted for exploratory laparotomy. During surgery, no masses were found in the pelvis; however, a 1-cm nodule was palpated in the left ovary and bilateral salpingo-oophorectomy was performed. On postoperative day 7, free and total testosterone levels decreased to 2.5 pg/mL (normal, < 6.9 pg/mL) and 19 ng/dL (normal, 3–46 ng/dL), respectively. The patient was discharged on postoperative day 10. At 4- and 10-month postsurgical follow-up, the free and total testosterone levels were within the normal range. Because total and free testosterone levels decreased within days of surgery and the normal levels were maintained through follow-up, the ovaries were confirmed as the source of androgen excess and the associated hyperandrogenic state.

The final pathologic examination was available 2 weeks after discharge and revealed an expansile, well-circumscribed nodular mass with a red-brown glistening surface measuring 1.5 × 1.5 × 1.2 cm confined to the hilum of the left ovary (**Figure 1**). This tumor was lobulated with patchy fibrous septae, consisting of aggregates of cells with abundant eosinophilic cytoplasm and round nuclei with prominent nucleoli (**Figure 2**). Immunohistochemical studies showed that the tumor cells were nonreactive with pancytokeratin and synaptophysin and weakly reactive with neuron-specific enolase and chromogranin. Reinke's crystals were identified, and the cells were strongly reactive to inhibin (**Figure 3**). The final diagnosis was Leydig cell tumor, hilar type.

DISCUSSION

Determining the cause of hirsutism can be challenging. In the case patient, the sudden worsening of hirsutism (ie, the patient progressed from not shaving at all, to shaving twice weekly, and to daily facial shaving) pointed towards a pathologic cause. As she was fertile in the past, PCOS and nonclassic congenital adrenal hyperplasia were unlikely causes. Given the patient's history, hirsutism caused by medication use was deemed unlikely. At this point, the differential also included other rarer causes of hirsutism including hyperthecosis and androgen-producing tumors. The next step was hormonal evaluation of the patient, which showed levels of testosterone 10 times the upper limit of normal but normal DHEA-S levels. These findings clearly pointed to an androgen-producing tumor as the likely cause. Hence, imaging studies were performed to determine the source of the androgen excess. The normal appearance of the adrenal glands on abdominal CT scan and the normal DHEA-S levels were instrumental in implicating the ovary as a source of the androgen excess. Pelvic ultrasonography was performed, as it is considered to be better than CT scan for detecting ovarian masses smaller than 1 cm. The final diagnosis was made by pathology.

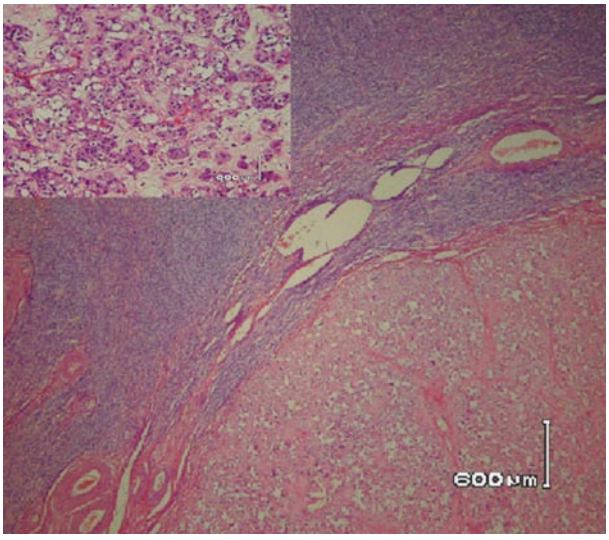

Figure 2. A high-power photomicrograph showing a pure Leydig cell tumor clearly separated from normal ovarian tissue by a fibrous capsule (hemotoxin and eosin stain, 10×). The inset shows large polygonal cells with round nuclei, a prominent nucleolus, and abundant clear or eosinophilic cytoplasm (hemotoxin and eosin stain, 40×).

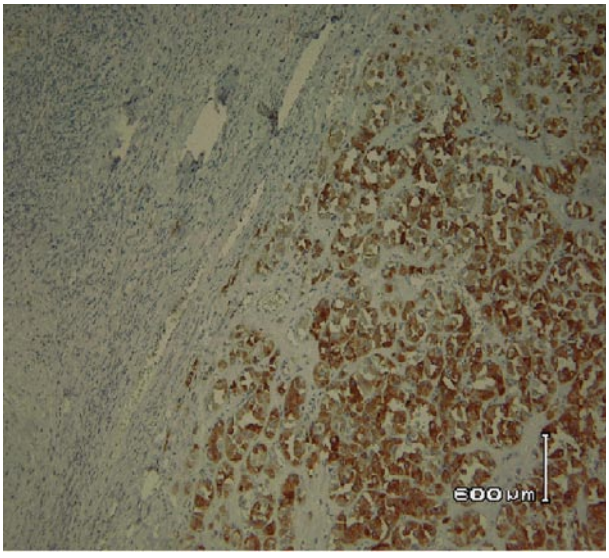

Figure 3. A high-power photomicrograph of the pure Leydig cell tumor showing intense cytoplasmic immunoreactivity to inhibin stain (inhibin stain, 10×).

ANDROGEN-SECRETING TUMORS

Classification

Most androgen-secreting ovarian tumors are sex cord-stromal tumors, which constitute less than 5% of all ovarian neoplasms.[11] According to the World Health Organization histologic classification of ovarian tumors, sex cord tumors can be classified as granulosa-theca cell stromal tumors, Sertoli-stromal cell tumors, sex cord tumor with annular tubules, gynandroblastoma, unclassified, and steroid cell tumors.[12] The Sertoli-stromal cell tumors consist of Sertoli-Leydig cell tumors, as well as pure Sertoli cell or pure Leydig cell tumors. Leydig cell tumors account for 15% to 20% of steroid cell tumors.[13] Roth and Sternberg[14] categorize pure Leydig cell tumors as either nonhilar Leydig cell tumor or hilar Leydig cell tumor. The nonhilar Leydig cell tumors are extremely rare (with only a handful of cases reported in the literature), are usually benign,[15,16] and typically occur in postmenopausal women.[17] They consist of 2 cell types: the Leydig cell and spindle-shaped stromal cells.[15,16]

Hilar Leydig Cell Tumor Histology

Hilar Leydig cell tumors are located in the hilus of the ovary and can extend into the ovarian stroma depending on the size of the tumor.[13] They are derived from large eosinophilic cells similar to those present in the ovarian hilus.[13] These tumors are generally benign and are usually unilateral.[18] Their mean diameter is between 2.4 and 2.7 cm.[13,19] Macroscopically, they are solid, fleshy, and well circumscribed; they appear yellow, orange, or more commonly brownish in color.[19,20] Reinke crystals, which must be present to classify the tumor as Leydig cell, are elongated, hexagonal eosinophilic crystals present in the cytoplasm or rarely in the nucleus; in their absence, the tumor would be classified as a steroid cell tumor not otherwise specified.[21] The Leydig cell tumor is mainly composed of diffusely arranged steroid cells with abundant eosinophilic cytoplasm, round hyperchromatic nuclei, and single small nucleoli. Other notable features of a Leydig cell tumor include nonmedullated nerve fibers, the tendency for cells to cluster around vessels, and fibrinoid necrosis of blood vessel walls.[19]

Presentation

Androgen-secreting ovarian tumors should be suspected clinically when the onset of androgenic symptoms is rapid and sudden; onset of hirsutism occurs in the third decade or later; onset is of short duration (< 1 yr); preexisting hirsutism displays sudden progressive worsening; symptoms and signs of virilization are present; and/or the testosterone levels are more than 3 to 4 times the upper limit of normal.[22] However, symptoms and signs associated with Leydig cell tumors may have a more gradual onset, with as much as 5 to 7 years between onset of symptoms and diagnosis.[18,23–26] At diagnosis, the mean age of women with Leydig cell tumor is

58 years.[13,19,27,28] Patients with Leydig cell tumors usually present with signs of virilization, including severe hirsutism, frontal balding, clitoromegaly, increased libido, altered body fat, increased muscle mass, breast atrophy, deepening of voice, and pustular acne.[13] Premenopausal patients also report amenorrhea or oligomenorrhea. Overt signs of hyperandrogenism are evident in more than 80% of patients.[13] Estrogenic manifestations, such as irregular menses or postmenopausal bleeding, have also been reported.[19,29,30]

It should be noted that virilization is highly suggestive of androgen-producing tumors but is not diagnostic as patients with HAIR-AN syndrome, PCOS, and hyperthecosis may also rarely present similarly.[31–33] PCOS is usually associated with younger age, increased follicle-stimulating hormone to luteinizing hormone ratio, menstrual irregularities, infertility, and enlarged cystic ovaries. HAIR-AN, which is considered to be a separate entity from PCOS, is usually found in younger women and is associated with insulin resistance and acanthosis nigricans. Ovarian hyperthecosis is found commonly in peri- or postmenopausal women with a history of long-standing hirsutism and is usually associated with a marked increase in the size of the ovaries.[22] In the case patient, the size of the ovaries was normal, and she had no signs or symptoms of insulin resistance.

Diagnosis

When establishing the diagnosis of hirsutism, it is important to consider the patient's race and ethnicity, as the amount of normal body hair for women varies. Clinically, women diagnosed with hirsutism usually score 8 or higher on the modified version of the Ferriman-Gallwey scale.[10] Measuring testosterone, DHEA-S, and 17-hydroxyprogesterone levels is useful for determining whether hyperandrogenism is responsible for the patient's hirsutism. Other tests such as 24-hour urinary free cortisol, prolactin level, and thyroid function tests can be performed to exclude Cushing's syndrome, hyperprolactinemia, and hypothyroidism if clinically indicated. Isolated elevation of testosterone without a corresponding increase in DHEA-S levels usually suggests the ovary as the source of the androgen excess.[24] Causes of increased testosterone production by the ovary include PCOS, hyperthecosis, and ovarian tumors. Adrenal tumors usually secrete DHEA-S in excess quantities, although there have been reports in the literature of adrenal tumors secreting mainly testosterone.[34] Tumors that produce testosterone usually do so in large quantities, and it is very common to find testosterone levels that are more than 3 to 4 times the upper limit of normal.[35]

Once testosterone has been identified as the cause of hirsutism, imaging is performed to localize tumors, if any are present. Abdominal CT scan for adrenal masses and pelvic ultrasonography for ovarian masses are good imaging modalities for diagnosis. Frequently, no mass is detected in the ovary on imaging, and exploratory laparoscopy or laparotomy is usually the next step. Alternative diagnostic approaches include catheterization of the ovarian and adrenal veins in order to localize the source of the androgen excess. However, this diagnostic tool remains an adjunctive method due to the high degree of expertise required to perform the procedure.[24,36,37] ^{18}Fluorodeoxyglucose positron emission tomography (FDG-PET) scan may be an emerging diagnostic modality, as Mattsson et al[38] report using FDG-PET to localize a testosterone-producing Sertoli-Leydig cell tumor.

Treatment

Treatment of an ovarian mass with total abdominal hysterectomy, bilateral salpingo-oophorectomy, and complete surgical staging should be carried out in an older woman not desiring fertility.[39] If fertility is desired, unilateral oophorectomy with close follow-up postoperatively is indicated. Despite the manifestations of obvious androgen excess, the endometrium also should be evaluated for hyperplasia or adenocarcinoma (both of which are associated with hilar Leydig cell tumors), especially if there has been abnormal uterine bleeding.[40,41] The clinical course of a Leydig cell tumor is unknown largely because of the rarity of this diagnosis; however, most tumors reported in the literature have been benign.[13] Therefore, if pathologic examination confirms that the tumor is benign, only hormonal follow-up is needed.[42]

CONCLUSION

Androgen-producing tumors rarely cause hirsutism but should be suspected in every woman with virilizing clinical symptoms and very high testosterone levels. Sertoli-Leydig tumors are larger and usually found easily on imaging, whereas hilar Leydig cell tumors are smaller and often difficult to find on imaging. If imaging is negative, a reproductive gynecology consult can be the next option. If the clinical suspicion is high, explorative laparoscopy/laparotomy is indicated. **HP**

Corresponding author: Ambika Babu, MD, John Stroger Hospital of Cook County, 1900 West Polk Street, Room 805, Chicago, IL 60612; Ambika_Babu@rush.edu.

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