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Case Report

The Hidden Source of Testosterone Hypersecretion in a Female—A 30-Year Journey

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Abstract

A Sertoli-Leydig cell tumor (SLCT) is a rare ovarian tumor that often excessively secretes testosterone and its precursor, leading to virilization in females. We present a case of a female patient with persistent, severe hyperandrogenism. Our patient had a history of left oophorectomy due to an ectopic pregnancy and initially presented with amenorrhea at the age of 30. Biochemical evaluations suggested ovarian hyperandrogenism. Despite the absence of an ovarian mass, she underwent a right oophorectomy and remained hyperandrogenic postoperatively. When she established care with our endocrinology clinic at the age of 58, she had more virilizing features and total testosterone levels ranging from 10.1 to 12.0 nmol/L (292-346 ng/dL; normal reference range for women: 0.07-1.56 nmol/L; 2-45 ng/dL). While biochemical evaluations were consistent with tumorous ovarian hyperandrogenism, ultrasound and computed tomography again failed to identify the source. Finally, an 18F-fluorodeoxyglucose-positron emission tomography/computed tomography revealed a mass in the left adnexa, and she underwent removal of the mass. The final pathology confirmed SLCT. The case highlights that SLCT may be small and slow-growing and not readily visible on conventional imaging modalities.

Key Words: hyperandrogenism, menopause, Sertoli-Leydig cell tumor, positron emission tomography (PET)/computed tomography (CT)

Introduction

Sertoli-Leydig cell tumors (SLCT) are rare ovarian tumors arising from stromal cells and primitive sex cords in the ovary. These tumors represent less than 0.5% of ovarian tumors and typically occur between the second and fourth decades of life (1). Many of these tumors autonomously secrete testosterone or its precursor, androstenedione, which causes severe androgen excess in females. The rest of these tumors secrete estrogen or remain nonfunctioning (1, 2). The understanding of the prognostic factors of SLCT is relatively limited due to its rarity. Several studies have observed that tumor stage at the time of diagnosis and the degree of differentiation are the essential prognostic predictors (2-4). In women, serum testosterone usually reflects ovarian androgen production. A small amount of testosterone is also synthesized through the conversion of adrenal androgens (eg, androstenedione). Serum testosterone could be significantly elevated in adrenocortical cancer, where adrenal androgen precursor molecules are also invariably elevated in the circulation (1).

SLCT is usually large and readily palpable on pelvic exams at the time when patients seek medical assistance, and almost all the patients with SLCT have unilateral disease (1-3). Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are the conventional imaging modalities used to visualize the ovarian tumor (5). Here we present a case of a female with severe hyperandrogenism from a SLCT that took 3 decades to confirm and resolve as the tumor had not been detected by conventional imaging studies.

Case Presentation

A 58-year-old female was seen for unresolved hyperandrogenism. She first noted amenorrhea at the age of 30. Subsequently, she developed hirsutism with frontal baldness, clitoromegaly, a deepened voice, and masculinity over the next decade. The patient reported normal puberty and a history of regular menses. She achieved spontaneous pregnancies, which she carried to term for the first 2 and had an ectopic pregnancy for the third. She reported a history of left salpingo-oophorectomy when she was 24 years old, resulting from the ectopic pregnancy. Initial evaluations showed elevated testosterone and low LH. ACTH, cortisol, androstenedione, and 17-hydroxyprogesterone were normal. The initial pelvic ultrasound did not visualize ovarian or adnexal masses, nor did the abdominal and pelvic CT scans show any suspicious lesions. The patient underwent a right salpingo-oophorectomy when she was 45 years old to treat the unresolved hyperandrogenemia, which revealed normal pathology without resolution of her hyperandrogenism. The following transvaginal US showed a uterine fibroid but an absence of ovaries bilaterally. She was treated with GnRH analog for an unclear period without clinical improvement of hyperandrogenism, which was discontinued as she lost follow-up with the initial endocrinology clinic.

Diagnostic Assessment

Since establishing care in our endocrinology clinic due to changing insurance, her total testosterone ranged from 10.1

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to 12.0 nmol/L (292–346 ng/dL) (normal reference range for women: 0.07-1.56 nmol/L; 2-45 ng/dL), FSH was 1.4 IU/L (1.4 mIU/mL) (normal reference range for postmenopausal women: 23.0-116.3 IU/L; 23.0-116.3 mIU/mL), and LH was 0.5 IU/L (0.5 mIU/mL) (normal range for postmenopausal women: 10.0–54.7 IU/L; 10.0-54.7 mIU/mL). Her morning ACTH was 9 ng/dL (9 pg/mL) (normal reference range: 6-50 ng/dL; 6-50 pg/mL), morning cortisol was 386.4 nmol/L (14.0 mg/dL) (normal reference range: 110.3-608.0 nmol/L; 4-22 mg/dL), dehydroepiandrosterone was <0.69 nmol/L (<20 ng/dL) (normal reference range for postmenopausal women: 2.67-29.53 nmol/L; 77-851 ng/dL), dehydroepiandrosterone sulfate ranged from 0.45 to 0.78 mmol/L (17-29 mcg/dL) (normal reference range: 0.32-3.59 mmol/L; 12-133 mcg/dL), androstenedione ranged from 1.32 to 1.85 nmol/L (38-53 ng/dL) (normal reference range for postmenopausal women: 0.70-2.62 nmol/L; 20-75 ng/dL), dihydrotestosterone was 0.59 nmol/L (17 ng/dL) (normal reference range: <0.69 nmol/L; <20 ng/dL), estradiol was 124.8 pmol/L (34 pg/mL) (normal reference range for postmenopausal women: <113.8 pmol/L; <31 pg/mL), and sex hormone binding globulin was 26 nmol/L (normal reference range: 14-73 nmol/L). The patient underwent a low-dose dexamethasone suppression test, for which the patient was instructed to take dexamethasone 0.5 mg every 6 hours for 8 doses, then to obtain morning fasting blood work. There was no suppression of testosterone level after dexamethasone, suggesting the source of testosterone was an adrenal or ovarian tumor rather than a nontumorous etiology. The repeat abdominal and pelvic CT scan was unremarkable. An abdominal MRI showed no adrenal lesions. Finally, an 18F-fluorodeoxyglucose positron emission tomography (PET)/CT scan showed a 2.7 cm by 1.6 cm ellipsoid structure in the left ovarian bed (Fig. 1A) with a small area of hypermetabolic focus at the periphery of the structure with maximal standardized uptake values of 8.0 (Figure 1B).

Treatment

The patient eventually underwent removal of the left adnexal mass detected by the PET/CT scan via robotic-assisted left oophorectomy. In the laparoscopic survey, the left ovary was approximately 3 by 4 cm with a smooth surface and was densely adherent to the ovarian fossa.

Outcome and Follow-up

The pathology showed a tumor localized near the hilar aspect of the ovary. The cellular morphology and immunophenotype were consistent with a diagnosis of Leydig cell tumor. The cells were diffusely positive for calretinin, which is normally present in Leydig cells. The tumor measured up to 1.8 cm in its greatest dimension. Pelvic washings did not show malignant cells. There was no expression of Ki67, indicating the benign nature of this tumor. The postoperative total testosterone level dropped to 0.17 nmol/L (5 ng/dL) and remained around this level 9 months after the surgery. Clinically, the patient had growth of thin hair on the scalp, slowdown of body hair growth, and reduction of clitoral size in the 6- to 9-month postoperative period.

Discussion

Androgen-secreting tumors account for 0.2% of androgen-excess disorders in females, and ovarian SLCT constitutes <1% of all ovarian cancers (1). SLCT can occur in both premenopausal and postmenopausal females, with a reported median age of 44 and 45 years in 2 recent studies (2, 3). Depending on whether and which hormone(s) the ovarian tumor is producing, patients may or may not present with virilization symptoms. With excessive androgen production, female patients often present with rapidly progressing virilization. Patients whose tumor also secretes estrogen are at risk of endometrial hyperplasia and endometrial cancer. Our patient has not had elevated estradiol levels proportional to her hyperandrogenism.

Conditions that manifest with endogenous hyperandrogenism in women of reproductive age include polycystic ovary syndrome, ovarian tumor, nonclassical congenital adrenal hyperplasia, Cushing syndrome, glucocorticoid resistance, adrenal tumor, luteoma of pregnancy, hyperreactio luteinalis, aromatase deficiency in fetus, hyperprolactinemia, and others (1). Some of these have tumorous etiologies, while the others do not. In a study evaluating the value of low-dose dexamethasone in suppressing adrenal testosterone production, Kaltsas et al demonstrated that 88% of the female patients with nontumorous hyperandrogenism were able to achieve normalization, or 40% and greater suppression of testosterone production (6). In our patient, after administering 0.5 mg dexamethasone every 6 hours for 48 hours, her testosterone remains elevated at 346 pg/dL, suggesting a tumorous etiology.

Testosterone and androstenedione production could come from both the adrenal gland and the ovary, and it is crucial to differentiate the ovarian origin of androgen excess from the adrenal origin. Selective ovarian/adrenal venous catheterization and hormonal sampling may be a method for diagnosing and localizing SLCT. However, the procedure is invasive, and successful catheterization could be challenging (7, 8). The accuracy rate to localize ovarian androgen-producing tumors is reported at 66% (9). Given the invasive nature and the reported history of bilateral oophorectomy, our patient did not pursue this procedure.

High-resolution transvaginal ultrasound (TVUS) remains the primary imaging modality for the evaluation and characterization of adnexal lesions with high sensitivity and specificity (5). CT has poor contrast resolution of adnexal structures but excellent visualization of calcium- and fat-containing masses (7). Hence, CT is the preferred imaging modality for detecting adrenal tumors. On the other hand, MRI characterizes soft tissue well and has superior contrast resolution. The contrast-enhanced MRI has shown a higher positive and negative predictive value for detecting an androgen-secreting ovarian tumor than TVUS (10). Our patient had undergone multiple imaging evaluations, including TVUS, abdominal and pelvic CT, and abdominal MRI scans, without successful localization of the lesion, despite clinical assessments and biochemical evaluations suggesting SLCT. Finally, the PET/CT scan demonstrated an area of hypermetabolic activity in the left adnexal area, which was found to be a Leydig cell tumor by pathology study after its resection. It is possible that the CT scan missed the ovarian lesion in our patient due to the small size of the tumor, and, in retrospect, the abdominal MRI did not include the pelvic area.

A case resembling ours was also documented by Kong et al (11). In their report, a 51-year-old woman presented with signs and symptoms of hyperandrogenism persisting for 18 months, raising concerns about the presence of an androgen-producing

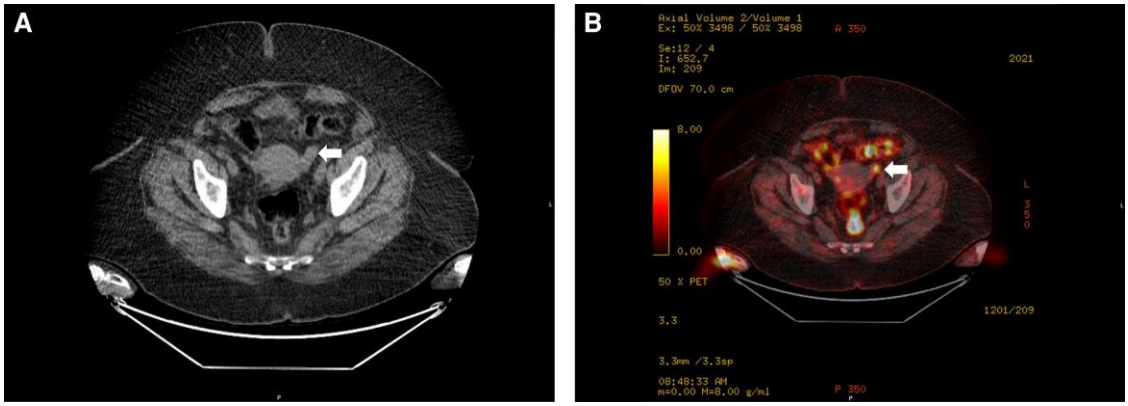

Figure 1. 18F-fluorodeoxyglucose PET/CT, skull base to thigh. (A) CT scan showing a left adnexal mass as identified by the white arrow; (B) PET scan showing a left adnexal mass with hypermetabolic activity as identified by the white arrow.

Abbreviations: CT, computed tomography; PET, positron emission tomography.

tumor. Despite clinical features and markedly elevated serum testosterone levels strongly suggesting an androgen-producing tumor, the TVUS, CT scan, and MRI failed to identify any discernible lesions. Ultimately, an 18F-fluorodeoxyglucose PET/CT scan revealed a minor area of increased uptake in the right adnexa, which was subsequently confirmed to be a 1.5 cm Leydig cell tumor. It can be challenging to confirm the presence of a small ovarian tumor with conventional imaging modalities, despite the clear suggestion from the biochemical findings. Both CT and MRI could be inadequate imaging modalities for a small ovarian tumor, as reported by Kong et al (11). In both our case and the one reported by Kong et al, small Leydig cell tumors, each measuring less than 2 cm in diameter, were ultimately diagnosed (11). Our patient and the 2 other published case reports demonstrated the utility of PET/CT scans in detecting small SLCTs in the ovary (11, 12). Notably, our patient experienced hyperandrogenism for 3 decades before a 1.8 cm well-differentiated Leydig cell tumor was finally identified, suggesting an exceptionally slow growth rate for this tumor in our patient's case.

It is worth highlighting that well-differentiated sex cord-stromal SLCT represents the least common variety among the 3 SLCT variants, which include well-differentiated, moderately differentiated, and poorly differentiated. While the DICER1 mutation is present in SLCT, it is more prevalent in the moderately and poorly differentiated variants rather than in the well-differentiated type. This discrepancy may suggest that well-differentiated SLCT is a distinctive category in the class of SLCT tumors (13).

When a female patient presents with hyperandrogenism, careful biochemical evaluations should be carried out to determine the source of excessive androgen. While an SLCT is often readily seen in conventional imaging studies such as US, MRI, or CT scans due to its large size at the time of presentation, a PET/CT scan can be a useful tool to detect it when the lesion is small.

Learning Points

- Small SLCT tumors could be challenging to localize by conventional imaging.
- The low-dose dexamethasone suppression test can be used to help differentiate nontumorous hyperandrogenism from tumorous hyperandrogenism from adrenal or ovarian etiology.
- When conventional imaging modalities cannot localize the source of androgen hypersecretion, PET/CT should be considered.

Contributors

Both authors made individual contributions to authorship. A.Y. and I.M. were involved in the diagnosis and management of this patient and manuscript submission. Both authors reviewed and approved the final draft.

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Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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