Clinical Case Report

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# An ovarian Leydig cell tumor of ultrasound negative in a postmenopausal woman with hirsutism and hyperandrogenism

## A case report

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**Abstract**

**Rationale:** The incidence of severe hyperandrogenism associated with masculinity in women is very low. While rare and difficult to diagnose, androgen secreting tumors should be suspected in women with hyperandrogenism and hirsutism, especially in the postmenopausal population. Herein we present one case of ovarian Leydig cell tumor (LCT) with markedly elevated serum testosterone levels and frank hirsutism.

**Patient concerns:** A 60-year-old woman, presented with increased hair growth and androgenic alopecia and the hormonal laboratory examination showed that she had elevated serum testosterone level and normal dehydroepiandrosterone sulfate (DHEAS), androstenedione, 17- hydroxyprogesterone, cortisol and thyroid stimulating hormone (TSH).

**Diagnoses:** The diagnosis of possible testosterone secreting tumor was performed when pelvic computed tomography (CT) and magnetic resonance image (MRI) showed a right adnexal mass of 15mm×16mm indicative of sex cord- stromal tumors.

**Interventions:** The patient received laparoscopic total abdominal hysterectomy and bilateral salpingo-oophorectomy.

**Outcomes:** After operation, testosterone got back to the normal level and clinical symptoms subsided.

**Lessons:** It is common that postmenopausal androgen excess is a state of relative or absolute androgen excess originating from the adrenal gland and/or ovaries. In either case, doctors need to assess such patients and exclude relatively rare potential causes of tumors. Any woman who has hirsutism or frank evidence of markedly increased testosterone should exclude this kind of possibility of androgen producing tumors. It is possible to determine the origin of androgen hypersecretion with the severity of symptoms, the extent of androgen excess, and the relevant imaging studies. Since LCT are rare ovarian sex-cord stromal tumors, it can be beneficial for diagnosis with careful research of patient history of the defeminization followed by virilization, and a CT and MRI image.

**Abbreviations:** DHEA = dehydroepiandrosterone, DHEAS = dehydroepiandrosterone sulfate, LCT = Leydig cell tumor, MRI = magnetic resonance image.

**Keywords:** hyperandrogenism, Leydig cell tumor, ovarian tumor, postmenopause, testosterone

## 1. Introduction

It is challenging to diagnose postmenopausal hyperandrogenism disease, because this disease is more considered to be a cosmetic show (excessive hair growth) due to normal hormonal changes with aging instead of true endocrine complaints. The rapid decline in estrogen levels was associated with a decrease in the sex hormone binding globulin,[1] while androgen secretion gradually decreased with aging, and maintained to a low level until the late stage of life.[2] The rapid progression of hirsutism, defined as the presence of terminal hair in androgen-dependent body regions, and other manifestations of androgen excess in a postmenopausal woman (such as acne and alopecia) strongly indicate the need to be suspicious of potential adrenal or ovarian tumor.[3] Differential diagnoses include undiagnosed aggravated hyperandrogenic disorders such as polycystic ovary syndrome, congenital adrenal hyperplasia, ovarian hyperthecosis, hyperandrogenic insulin-resistant acanthosis nigricans syndrome, androgen-secreting neoplasms, idiopathic hirsutism, Cushing syndrome, and iatrogenic hyperandrogenism.[4]

The ovarian sex cord-stromal tumors are relatively rare, only accounting for 5% to 8% of all ovarian neoplasms, often originate from the sex cord cells which surround the oocytes, but

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also partly derived from the stroma, and less than half can secrete androgen.[5] Leydig cell tumors (LCTs), which originate from ovarian sex cord stroma and comprise less than 0.1% of all ovarian tumors, occur more commonly after menopause.[6] Their unregulated testosterone secretion results in hyperandrogenism and virilization.[7]

The diagnosis of these rare tumors may be difficult especially in cases of not clear palpation of ovarian tumors with negative ultrasound images. Herein, we report 1 case with markedly elevated testosterone levels and frank hirsutism, and the patient was found to have right ovarian LCT.

## 2. Case report

This study was carried out in accordance with the Helsinki Declaration and approved by the Institutional Review Board. Informed consent was gotten before the study. A 60-year-old Chinese female with hirsutism was referred to the Department of Endocrinology for 6 months. She did not smoke or drink. She had a past history of cured pulmonary tuberculosis and well-controlled type 2 diabetes mellitus with Metformin (500 mg, twice a day), and Glimepiride (2 mg, once before breakfast) but without any medication of androgenic effects. The patient had achieved menopause at the age of 53 without postmenopausal bleeding. Her menarche was at age 15 and she had a normal menstrual history before menopause. She was gravida 3 parity 3. Her weight was 60 kg, height 1.58 m with body mass index of 24 kg/m$^2$. Abdominal examination revealed no mass, and there was no significant difference in gynecologic assessment. Physical examination revealed the patient had signs of virilization, including coarse hair along her upper lip, chin, lower abdomen and inner thigh with Ferriman–Gallwey score of 8, frontal balding, and coarse facial features. No acne, voice hoarseness, clitoromegaly, and other virilization signs was found. She had no signs of acanthosis nigricans syndrome, or Cushing syndrome.

The hormonal test showed that she had high total testosterone levels (399.9 ng/dL, normal range 14–76). Her androstenedione (1.6 ng/mL), dehydroepiandrosterone sulfate (DHEAS) (114.6 μg/dL), estradiol (51 pg/mL), 17-hydroxyprogesterone (1.72 nmol/L), prolactin (4.4 ng/mL), and thyroid stimulating hormone (1.958 mU/L) were at normal ranges. The levels of cortisol were also normal and ovarian tumor markers of cancer antigen 125, carcino-embryonic antigen, and cancer antigen 199 were below reference values.

Despite biochemical androgen assessment of the ovarian origin, the diagnosis failed to localize the source of hyperandrogenism and several vaginal ultrasound did not detect adnexal mass. The repeated laboratory tests confirmed that her high testosterone levels were within the tumor range. A dexamethasone test (0.75 mg, 4 times a day for 5 consecutive days) was also conducted and the result revealed that the testosterone value did not decrease (244 ng/dL).

After pelvic computed tomography and magnetic resonance image (MRI) confirmed a well-circumscribed right ovarian nodule about 1.5 × 1.6 cm (Fig. 1A and B), the patient received laparoscopic total abdominal hysterectomy and bilateral sal-

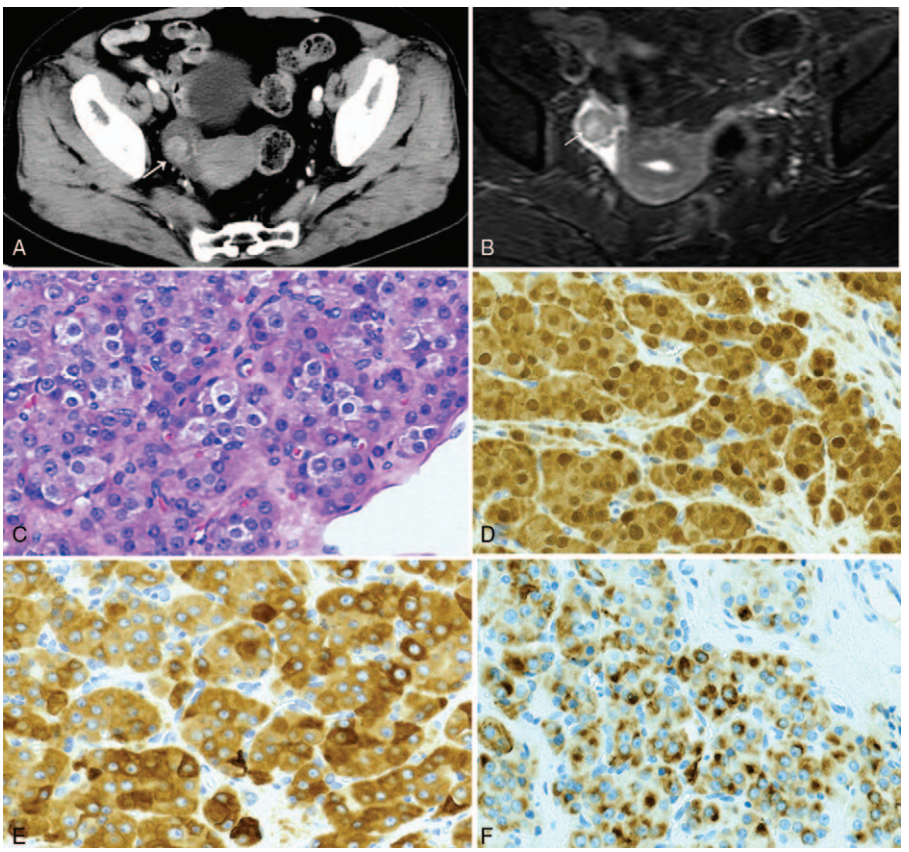


**Figure 1.** Pelvic CT (A) and MRI (B) identified a well-circumscribed, right ovarian nodule, 1.5 × 1.6 cm in diameter; microscopic hematoxylin-eosin, original magnification × 200 (C); immunohistochemistry showing neoplastic cells that stained positive for CR (D), inhibin α (E), and CK (pan) (F). MRI = magnetic resonance image, CK = cytokeratin, CR = calretinin, CT = computed tomography.

pingo-oophorectomy. The ovarian venous blood was not sampled during the operation. In the laparotomy, the left ovary and the uterus were normal. The right ovary was slightly enlarged showing a grayish-white solid nodule with a diameter of about 1.7 cm. No ascites or peritoneal lesions were observed. The histopathology confirmed an LCT located in the stroma of the right ovary. Microscopic characters of the tumor were described as follows (Fig. 1C): nests, trabecular, clusters of rounded to polygonal cells with moderately sized, vesicular, central nuclei and eosinophilic, granular to finely vacuolated cytoplasm matched with LCT, and no definitive pathognomonic rod-shape Reinke crystals were identified. Mitotic figures were inconspicuous and necrosis was not identified. The immunohistochemistry indicated positive staining for calretinin, inhibin α, and cytokeratin pan (Fig. 1D–F), while the staining for chromogranin A, S-100, cluster differentiation 99, and smooth muscle actin were negative. The testosterone levels (57.1 ng/dL) dropped significantly postoperatively. During the 6-month follow-up, the patient kept in good health with significantly improved signs of virilization.

## 3. Discussion

The differential diagnosis of hyperandrogenism for a postmenopausal woman includes androgen-producing ovarian and adrenal tumors, Cushings syndrome, partial congenital adrenal hyperplasia, and iatrogenic causes such as medication. Sertoli–Leydig cell tumors, LCT, steroid cell tumors not otherwise specified, and gynandroblastomas are the usual androgen producing ovarian tumors.[3] The comprehensive clinical history and detailed physical examination are necessary for these patients to obtain the accurate diagnosis.[3] The patient's normal menstrual cycle and no clinical signs of hyperandrogenism in the childbearing age exclude the possibility of delayed diagnosis of congenital adrenal hyperplasia or polycystic ovary syndrome. Her normal weight before and after menopause makes these diseases more unlikely.[8] Hyperandrogenism with rapidly progressive hirsutism (a Ferriman–Gallwey score value >8) or virilization signs indicates tumor etiology.[3] A woman of hyperandrogenism with much higher serum testosterone levels than the normal range is often considered to have ovarian or adrenocortical tumors.[9] The clinical characteristics of female virilization may manifest with hirsutism, muscularity, forehead baldness, clitoromegaly, acne, coarse voice, and abnormal menstruation.[10] These changes are caused by elevated androgen including testosterone, dehydroepiandrosterone (DHEA), and DHEAS. The normal female produce testosterone 0.1 to 0.4 mg a day, with one fourth being secreted by the ovaries, one quarter by the adrenals and a half metabolized from the peripheral prehormones.[11] On the contrary, DHEA is mainly produced by the adrenal glands (50%), with the ovaries and peripheral transformation from circulating DHEAS accounting for 20% and 30%, respectively. More than 200 ng/dL testosterone concentrations or 47,000 ng/mL DHEAS (tumor range) imply the requirement for further study.[12] The testosterone of this patient was within the tumor level, while DHEAS was within the normal range. Because of the limitation of basal serum testosterone in identifying patients harboring virilizing tumors, the testosterone response to dexamethasone administration has been used to improve the diagnostic accuracy of androgen producing tumors.[13] The plasma cortisol levels decreased, but total testosterone suppression did not occur after the dexamethasone test. Combined with other biochemical data, such as the lack of co-secretion of cortisol and DHEAS, the origin of ovarian tumor was hinted,[3] which was verified by surgery and postoperative normal testosterone levels.

Ovarian tumors, which secreting androgen, are usually small and often embedded in the ovary with a polycystic appearance may be missed if no sensitive detection instrument is applied.[13] Transvaginal color doppler ultrasound is very useful in the discovery and diagnosis of ovarian tumors.[14] However, in our case, repeated transvaginal ultrasound failed due to the LCT was isoechoic to the uterus, while computed tomography and MRI scan showed a contrast enhanced right adnexal mass. It is proposed that in the differential diagnosis of ovarian tumors the sensitivity and specificity of MRI may be better than ultrasound, as shown by the 78% positive and 100% negative predictive value in a large and detailed study evaluating postmenopausal hyperandrogenism with and without tumors.[15] In magnetic resonance imaging, the T1-weighted signal intensity of ovary tumors is low, and the T2-weighted signal varies according to the interstitial tissue contents of stroma.[16] Positron emission tomography scanning has shown testosterone secreting ovarian tumors with high uptake of 18F-2-fluorodeoxy-D-glucose even if other imaging techniques are negative.[17] Although 5 cases of bilateral tumors are reported in the literature, LCT is unilateral 95% of the time, which raises the debate of selective ovarian venous sampling.[18] Given the tendency toward bilateral resection, we agree against the general use of diagnostic catheterization, although perhaps it could play a beneficial role in women of reproductive age.[19]

The Leydig cells that have the potential to secret androgens are distribute in more than eighty percent of all female ovaries. Nodules of Leydig cells over 1 cm are usually defined as LCT, while less than 1 cm are called hyperplasia, but the distinguish between them is difficult.[20] The pathogenesis of Leydig cell proliferation and LCT is unclear, but the current opinion is that it might be either autonomous developed or by central stimulation, such as elevated LH in postmenopausal women. According to the most probable source of tissue, World Health Organization has sorted ovarian tumors into surface epithelial (65%), germ cell (15%), sex cord-stromal (10%), metastases (5%), and miscellaneous.[5] The stromal LCT, as the rarest subtype of an already rare subdivision of ovarian germ cell tumor, is extremely rare, with androgenic function that usually occurs in postmenopausal women.[5] Although LCTs are typically benign with excellent prognosis, it is a diagnostic challenge to detect on multiple imaging modalities as LCT are typically <4 cm in size.[21] A laparoscopic bilateral salpingo-oophorectomy was carried out, and histopathological examination and immunohistochemistry verified the diagnosis of an LCT. Among the numerous immunohistochemical markers of ovarian tumors, inhibin and calretinin are most helpful, since many steroid cell tumors express these markers.[22] Epithelial membrane antigen is particularly useful in differentiating ovarian or renal clear cell carcinoma from steroid cell tumors, since the expression of epithelial membrane antigen most occurred in carcinomas, while not in most steroid cell tumors.[22]

In conclusion, we report 1 case of LCT in a postmenopausal woman presenting with hirsutism. Although rare and difficult to diagnose biochemically or with imaging studies, androgen secreting tumors should be considered in women (especially if she was postmenopausal) with hyperandrogenism and hirsutism. In fact, diffuse stromal Leydig cell hyperplasia and LCTs (usually small) may escape from imaging and in some cases only pathology can confirm the result. Therefore, it is suggested that laparoscopic bilateral oophorectomy is a recommended

therapeutic method for postmenopausal women with the suspected ovarian origin to hyperandrogenism. This treatment could also be applied to premenopausal women that have completed their fertility. Compared with hormone therapy, this treatment has the merits of clear diagnosis, higher compliance rate, and less follow-up. So, it has better cost-effectiveness.

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