

Accessory ovarian steroid cell tumor producing testosterone and cortisol

A case report

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Abstract

Rationale: An accessory ovary is a rare structure containing normal ovarian tissue, which has a direct or ligamentous connection with a normal and eutopic ovary.

Patient concerns: In the study, we reported a 46-year-old woman presented with secondary amenorrhea and virilization symptoms for 1 year.

Diagnoses: Endocrine evaluation revealed slightly elevated serum cortisol, extremely elevated 24-hour urinary-free cortisol and serum testosterone. Clinical assessment exhibited a large solid mass with heterogeneous enhancement in the left adnexa, compounded with hypercortisolism and hyperandrogenemia. An accessory ovarian tumor attached to the infundibulum of the left fallopian tube was found, and a separate normal ovary was present on the same side.

Interventions: The patient underwent a left adnexectomy.

Outcomes: During surgery, a 12 cm × 8 cm, gray-red, and well-circumscribed solid mass was identified. The tumor had ligamentous attachment with the infundibulum of left fallopian tube. The sectioned surface was gray-brown, lobulated and did not exhibit either significant necrosis or hemorrhage. Pathological findings demonstrated that tumor cells had small round nuclei, mild atypia, no mitosis were arranged in a diffuse pattern of columns or nests separated by a rich vascular network and no crystals of Reinke were found. It was diagnosed as ovarian steroid cell tumor (NOS) without malignant behavior by immunohistochemical staining. The patient was finally diagnosed as accessory ovarian steroid. The patient was discharged from the hospital on the seventeenth day after surgery. During postoperative follow-up, the first postoperative menstrual flow recovered and blood pressure regained 1 month after surgery. Furthermore, her Cushing syndrome regressed and hirsutism disappeared completely 4 months after surgery.

Lessons: It is vitally important to establish a final diagnosis according to the clinical manifestations and laboratory values in addition to imaging studies and laparoscopic examination of a rare coexistence of hyperandrogenemia and Cushing syndrome based on the accessory ovarian pathology.

Abbreviations: ACTH = adrenocorticotropic hormone, LH = luteinizing hormone, CT = computed tomography, DHEA = dehydroepiandrosterone, EMA = epithelial membrane antigen, FSH = follicle-stimulating hormone, NOS = not otherwise specified, SCTs = steroid cell tumors.

Keywords: accessory ovary, Cushing syndrome, hyperandrogenemia, steroid cell tumor

Editor: Maohua Xie.

LZ and MY contributed equally to this work.

Ethics approval and consent to participate: Not applicable.

Consent for publication: Written informed consent was obtained by the patient for publication of this report and any accompanying images.

Authors' contributions: YMM and ZL conceived the case report. LZ, MY, GY, JL, ML, JD, WG, JD, WF, and YGM performed or participated in the examination. LZ and MY wrote the paper. YMM, ZL, LZ, MY, WF, and YGM interpreted the patient data. YMM, ZL, and NJ revised the manuscript. LY and JB searched the literatures. All authors read and approved the final manuscript.

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:37(e7998)

Received: 22 January 2017 / Received in final form: 8 August 2017 / Accepted: 15 August 2017

<http://dx.doi.org/10.1097/MD.0000000000007998>

Table 1**Hormone levels before and after surgery.**

| Hormone | Before surgery | | | After surgery | Normal values |
|-----------------------|----------------|----------------|-----------------|---------------|----------------------|
| | Baseline | After 4 mg Dex | After 16 mg Dex | | |
| Serum cortisol | | | | | |
| 8 AM | 555.46 | 544.55 | 556.31 | <25.7 | 198.7–797.5 nmol/L |
| 4 PM | 577.23 | | | <25.7 | 85.3–459.6 nmol/L |
| 0 AM | 576.38 | | | <25.7 | 0–165.7 nmol/L |
| Plasma ACTH | | | | | |
| 8 AM | <1.1 | 1.36 | 2.73 | 3.49 | <10.12 pmol/L |
| 4 PM | 1.42 | | | 3.6 | |
| 0 AM | <1.1 | | | 1.89 | |
| Urinary-free cortisol | 1742.2 | 964.5 | 1670.9 | 102 | 98.0–500.1 nmol/24 h |
| Serum testosterone | 36.83 | 33.69 | 34.86 | <0.35 | 0.5–2.6 nmol/L |
| Serum 17-OHP | 2.347 | 3.234 | 2.842 | 0.057 | 0.1–0.8 ng/dL |
| Serum DHEA | 491 | 447 | 606 | <15 | 35–430 μg/dL |

17-OHP = 17-hydroxyprogesterone, ACTH = adrenocorticotropic hormone, DHEA = dehydroepiandrosterone.

1. Introduction

Steroid cell tumors (SCTs) are a rare subgroup of sex cord-stromal tumors of the ovary. It has 3 subtypes according to cellular origin: stromal luteoma arising from ovarian stroma, Leydig cell tumor arising from Leydig cells in the hilus, and steroid cell tumor (not otherwise specified, NOS) when the lineage is unknown.^[1] The NOS subtype can produce different steroids and in turn have widely variant clinical manifestations.^[2]

An accessory ovary, which is an ectopic ovarian tissue that has a direct or ligamentous attachment to the normal ovary, is an uncommon congenital anomaly of the female reproductive. It also has the potential for endocrine.^[3] Tumors at accessory ovaries, especially steroid cell tumors are extremely rare, with the last case presented more than a decade ago.^[3] Here, we present a rare case of accessory ovarian steroid cell tumor (NOS), attaching to the infundibulum of the left fallopian tube, which secreted both testosterone and cortisol causing hyperandrogenemia and Cushing syndrome.

2. Case report

A 46-year-old Chinese woman who presented with secondary amenorrhea and virilization symptoms for 1 year was admitted to our hospital. Physical examination revealed mild hypertension (146/94 mm Hg), plethoric face, hirsutism of the chin, excess hair growth on abdomen and clitoral hypertrophy. Baseline laboratory

test results showed mild hypokalemia (3.41 mmol/L) and relatively high urine potassium excretion (31.78 mmol/24 hours).

Endocrine evaluation revealed slightly elevated serum cortisol without rhythm, extremely elevated 24-hour urinary-free cortisol and serum testosterone. In addition, the dehydroepiandrosterone (DHEA) and 17-hydroxyprogesterone (17-OHP) were both elevated. Dexamethasone (4 and 16 mg) failed to normalize the elevated hormone labels (Table 1).

The plasma adrenocorticotropic hormone (ACTH) level was undetectable. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and estradiol were in the normal range. Tumor markers including carbohydrate antigen (CA)-125, CA-19-9, squamous cell carcinoma antigen and beta subunit of human chorionic gonadotropin were also within their normal ranges.

A solid movable mass of 8 cm × 4 cm × 4 cm was palpated in the left adnexa. Transvaginal ultrasonography showed an 8.8 cm × 6.1 cm × 6.5 cm well-circumscribed solid mass in the left adnexa, whereas the right ovary was normal (Fig. 1A). Pelvic contrast computed tomography (CT) showed a 9.5 cm × 5.5 cm × 5.0 cm solid mass with heterogeneous enhancement in the left hypogastrum (Fig. 1B, red arrow), while the adrenal CT showed bilateral adrenal atrophy (data not shown).

The patient underwent a left adnexectomy which identified a 12 cm × 8 cm, gray-red, and well-circumscribed solid mass. The tumor had ligamentous attachment with the infundibulum of left fallopian tube (Fig. 1C). The sectioned surface was gray-brown,

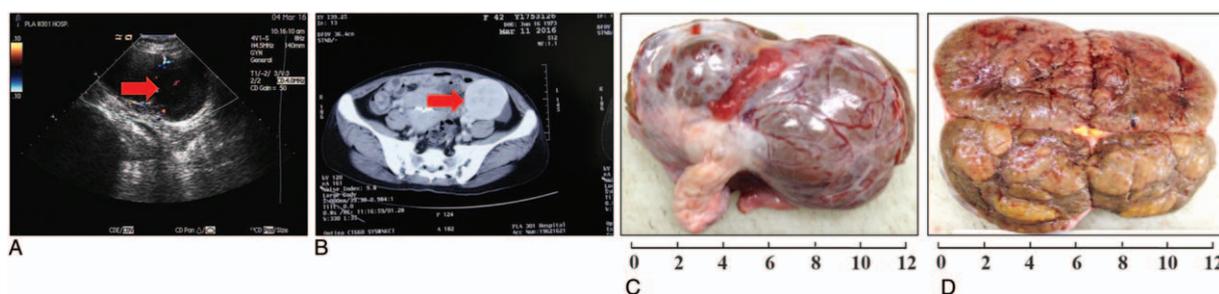


Figure 1. (A) Transvaginal ultrasonography showed (red arrow) an 8.8 cm × 6.1 cm × 6.5 cm well-circumscribed solid mass in the left adnexa, whereas the right ovary was normal. (B) Pelvic contrast computed tomography (CT) showed (red arrow) a 9.5 cm × 5.5 cm × 5.0 cm solid mass with heterogeneous enhancement in the left hypogastrum. (C) The tumor was a 12 cm × 8 cm, gray-red, and well-circumscribed solid mass and had ligamentous attachment with the infundibulum of left fallopian tube. (D) The sectioned surface of the tumor was gray-brown, lobulated and no significant necrosis and hemorrhage were observed.

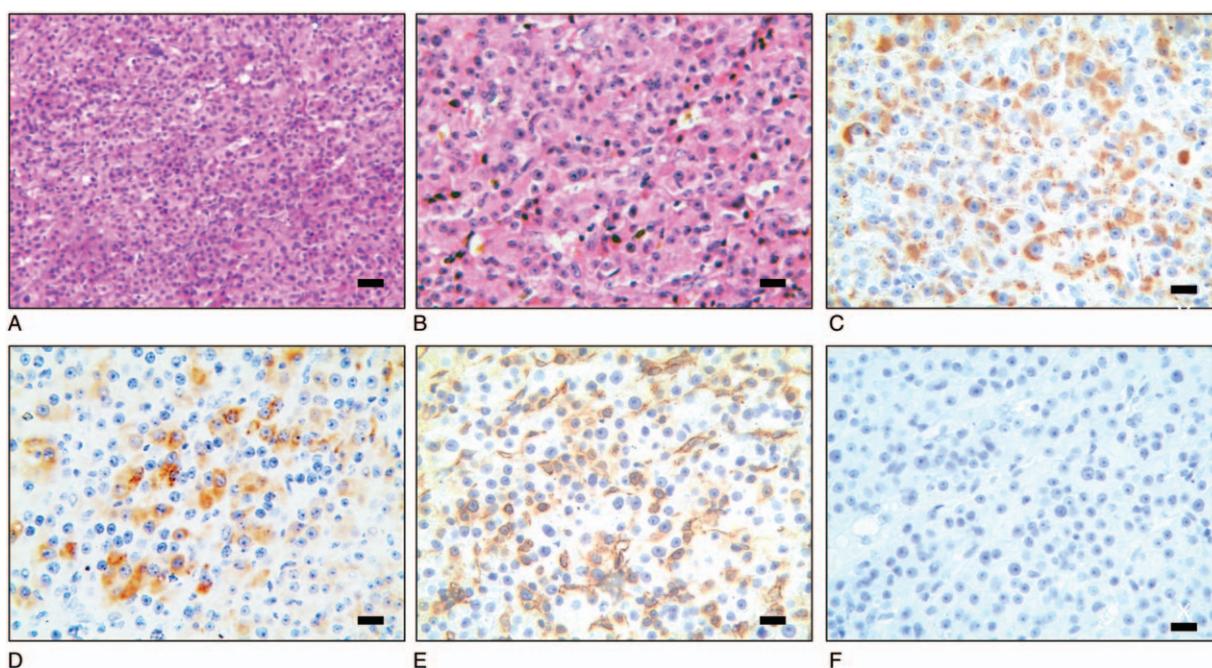


Figure 2. (A and B) Representative hematoxylin and eosin photomicrograph demonstrate tumor cells with small round nuclei, mild atypia, no mitosis. Tumor cells were arranged in a diffuse pattern of columns or nests separated by a rich vascular network and no crystals of Reinke were found. "A" and "B" represent images obtained at 20× and 40× magnification, respectively. (D–F) Immunohistochemical detection of calretinin (Abcam, ab702) (C), inhibin (Abcam, ab47720) (D), vimentin (Abcam, ab92547) (E), and epithelial membrane antigen (EMA) (Dako, Clone E29) (F) in 5 μm tissue specimen obtained from the accessory tumor. Scale bar represents 100 μm.

lobulated and did not exhibit either significant necrosis or hemorrhage (Fig. 1D). A separate normal ovary was present on the same side.

Pathological findings demonstrated that tumor cells had small round nuclei, mild atypia, no mitosis were arranged in a diffuse pattern of columns or nests separated by a rich vascular network and no crystals of Reinke were found (Fig. 2 A and B). Immunohistochemical staining for calretinin (Fig. 2C), inhibin (Fig. 2D), and the mesenchymal cell marker vimentin (Fig. 2E) was positive, and negative for epithelial membrane antigen (EMA) (Fig. 2F). The findings were consistent with the diagnosis of ovarian steroid cell tumor (NOS) without malignant behavior. The patient was finally diagnosed as accessory ovarian steroid cell tumor (NOS).

During the first 24 hours following surgery, the peripheral plasma cortisol became undetectable. Meanwhile, the peripheral serum testosterone, 17-OHP and DHEA fell to the normal range (Table 1). Prednisone (15 mg/day) was given to treat the temporary adrenal insufficiency. The patient was discharged from the hospital on the seventeenth day after surgery. During postoperative follow-up, the first postoperative menstrual flow recovered and blood pressure regained 1 month after surgery. Furthermore, her Cushing syndrome regressed and hirsutism disappeared completely 4 months after surgery. The patient has been asymptomatic after a follow-up of 1 year with normal serum testosterone (0.59 nmol/L) and without any evidence of recurrent tumor.

3. Discussion

Steroid cell tumors which were first described by Scully in 1979 account for less than 0.1% of all ovarian tumors.^[1] Among the 3 subtypes, steroid cell tumors (NOS) account for approximately

60% and usually occur in adults with an average age of 47 years.^[4] Most of the steroid cell tumors (NOS) have endocrine potentials and only 25% are nonfunctioning.^[1] Hirsutism and virilization are the most common symptoms occurring in 56% to 77% of patients. The serum total testosterone, DHEA and 17-OHP levels elevate markedly and cannot be suppressed by dexamethasone in these patients. The steroid cell tumors (NOS) have also been associated with Cushing syndrome in 6% to 10% of patients and estrogen secretion in 6% to 23% of patients.^[1] Steroid cell tumors (NOS) with multiple, simultaneous hormonal abnormalities are rare. An extremely rare case with hyperandrogenism, hypercortisolism, hyperestrogenemia, and hyperprolactinemia was though reported.^[5]

Steroid cell tumors (NOS) are usually well-circumscribed, occasionally lobulated and unilateral solid mass. Microscopically, they have a structure similar to adrenal zona glomerulosa and zona fasciculata, that is, smaller cells that have eosinophilic granular cytoplasm, and large, round to polyhedral cells with vacuolated cytoplasm are usually diffusely arranged in nests, clusters, cords or columns. Most of the steroid cell tumors are positive for calretinin and inhibin,^[6] while negative for EMA in immunohistochemical staining,^[7] which was mimicked in the patient discussed herein.

Accessory ovary, with a prevalence of 1/29,000 to 700,000 in the rarest congenital gynecological abnormalities, was defined as the third ovary with direct or ligamentous connection to the eutopic ovary. Tumors at accessory ovary are proportionately rarer than what happens in normal ovaries, not to mention the steroid cell tumors (NOS) with endocrine potentials.

The first case of steroid cell tumor (NOS) arising in an accessory ovary with hyperandrogenism was described more than a decade ago.^[3] Our patient had extremely elevated 24-hour urinary-free cortisol and serum testosterone, in addition to the

serum DHEA and 17-OHP which could not be suppressed by dexamethasone. These data collectively indicated the diagnosis of adrenocortical carcinoma, the most common tumors that can secrete cortisol and testosterone simultaneously.

Imaging examination showed an atrophic adrenal gland and large neoplasms located in the left ovary, indicating that the tumor was the source of testosterone and cortisol. The diagnosis was supported by the fact that her symptoms of virilization and Cushing syndrome disappeared and serum testosterone and cortisol decreased significantly after the lesions were removed. During the operation, the neoplasms were found to have ligamentous attachment with the infundibulum of the left fallopian tube, while a separate normal ovary was present on the same side. The pathological findings demonstrated that the neoplasms shared the same microscopic characteristics with ovarian steroid cell tumors (NOS), and were positive for calretinin, α -inhibin, and vimentin, while negative for EMA, confirming the diagnosis of accessory ovarian steroid cell tumors (NOS).

Most of the steroid cell tumors (NOS) are benign, while malignancy has been reported in as many as 25% to 43% of cases.^[8] Distant metastasis is the most direct evidence of malignancy. In addition, malignant neoplasms are commonly associated with identification of the pathological behaviors, such as the presence of equal to or greater than 2 mitoses per 10 high-power fields, vascular invasion, grade II or III nuclear atypia, and necrosis or hemorrhage with a diameter greater than 7 cm on gross pathologic specimen.^[1] Surgical intervention is the most effective treatment for steroid cell tumors (NOS) both in ovary and accessory ovary. Radiation or chemotherapy should be carried out if the neoplasms proved to be malignant or with distant metastasis. The pathological features of the accessory ovarian tumor of our patient suggested its benign behavior, although the size was larger than 7 cm. Thus further adjuvant chemotherapy was not given, and hormonal levels have been monitored as part of the patient's postoperative follow-up.

This case reports a rare coexistence of hyperandrogenemia and Cushing syndrome based on the accessory ovarian pathology. Accessory ovarian steroid cell tumors (NOS) with cosecretion of cortisol and androgen are extremely rare and represent a real diagnostic challenge for both clinicians and pathologists. As our case highlights, it is vitally important to establish a final diagnosis according to the clinical manifestations and laboratory values in addition to imaging studies and laparoscopic examination. Treatment should be individually based on tumor pathological and histological features and long term follow-up will be beneficial to these patients.

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