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Case Report

Testosterone-Secreting Endometrioid Ovarian Carcinoma Presenting With Hyperandrogenism

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ABSTRACT

Background/Objective: Epithelial cell ovarian carcinomas rarely secrete steroid hormones, while sex cord and stromal cell ovarian carcinomas often do so. The objective of this report is to describe a patient with endometrioid ovarian carcinoma, an epithelial cell tumor, who presented with hyperandrogenism due to testosterone production by the tumor.

Case Report: A 67-year-old postmenopausal woman with no history of endometriosis presented with new onset of hirsutism. Her testosterone level was 282 ng/dL (8-60 ng/dL), estradiol level was 72 pg/mL (≤32.2 pg/mL), and 17-hydroxyprogesterone level was 592 ng/dL (≤45 ng/dL). Pelvic ultrasound showed a right adnexal mass measuring 14.7 × 9.7 × 12.3 cm and an endometrial thickness of 9 mm with calcifications within the endometrium. Human epididymis protein 4 level was 210 pmol/L (0-140 pmol/L), and cancer antigen 125 level was 144 U/mL (0-34 U/mL). The patient underwent exploratory laparotomy with removal of the pelvic mass. Pathology showed an endometrioid adenocarcinoma with positive immunohistochemistry staining for the following steroidogenic enzymes: side-chain cleavage enzyme, 17α-hydroxylase, and aromatase. There was no evidence of tumor metastases within the pelvic cavity. Ovarian tumor markers normalized and remained stable 1 year after surgery.

Discussion: Although endometrioid ovarian carcinomas do not typically produce clinically significant levels of sex steroids, in rare cases, these tumors can do so, leading to symptoms and promoting early detection and treatment of the cancer.

Conclusion: Sex hormone secretion by epithelial cell ovarian carcinomas should be considered in cases of new-onset steroid hormone excess in postmenopausal women.

Introduction

Ovarian cancer is broadly categorized according to its origin from epithelial cells, germ cells, or sex cord and stromal cells of the ovary.[1] Epithelial cell ovarian cancers are further classified histologically into endometrioid, clear cell, high-grade serous, low-grade serous, mucinous, and other types of cancers.[1] Endometrioid ovarian cancer is associated with endometriosis in almost one-third of cases,[1,2] though it presents on average decades later (mean age at diagnosis of endometrioid carcinoma is 60 years[3] versus 34 years for endometriosis[4]). Unlike some other types of epithelial cell ovarian cancers, endometrioid carcinoma is often diagnosed in early disease stages[1,5,6] and has a relatively favorable prognosis.[7] Epithelial cell tumors usually do not produce sex steroids.[8,9] For example, in 2 recent, single-center studies, none of the 44 patients with virilizing ovarian tumors were found to have an epithelial cell carcinoma.[10,11] Presenting symptoms of epithelial cell carcinomas are commonly due to mass effect, obstruction of gastrointestinal and genitourinary tracts, and ascites.[12,13] Among epithelial cell tumors, mucinous tumors are the most common type to demonstrate steroid hormone production.[14] On the other hand, sex cord and stromal cell cancers of the ovary do often produce hormones, as they are derived from steroidogenic cells (granulosa, Sertoli, theca, and Leydig).[15] These tumors often present with symptoms of hormone excess, are diagnosed in early disease stages, are low-grade, and carry a good prognosis.[5] Hormone-secreting

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ovarian cancers are often associated with elevated levels of inhibins. This applies mainly to sex cord and stromal cell cancer, as well as some epithelial ovarian cancers.[16-18] Herein, we describe a patient with an inhibin-A-producing, endometrioid, ovarian carcinoma, a type of epithelial cell cancer, who presented with hyperandrogenism due to testosterone production by the tumor.

Case Report

A 67-year-old Caucasian woman with a past medical history of hyperlipidemia and hypertension was referred to the endocrinology clinic for evaluation of new-onset hyperandrogenism. She complained of hirsutism on her cheeks, neck, and arms of 6 months' duration, as well as a weight gain of 5 pounds. She denied any voice changes, increased libido, or clitoromegaly. Bowel and bladder functions were normal. The review of systems was otherwise normal. Surgical history was notable for a prior uterine myomectomy for benign fibroids and a parathyroidectomy for hypercellular parathyroid, but no history of osteoporosis, bone fractures, or nephrolithiasis. The patient was postmenopausal and had 3 children. She was a retired teacher with no history of smoking or alcohol use. Family history was notable for colon cancer in the patient's father, diagnosed at age 55. At the time of evaluation the patient was being treated with atorvastatin 20 mg daily and irbesartan 150 mg daily. Her blood pressure was 120/70 mm Hg, pulse was 80 beats/min, and body mass index was 34 kg/m^2. Physical examination was notable for hirsutism. There was no facial plethora, dorsocervical adipose hypertrophy, striae, clitoromegaly, or palpable adnexal masses. Laboratory evaluation showed marked elevations in the testosterone level (282 ng/dL; normal postmenopausal range, 2-45 ng/dL), estradiol level (72 pg/mL; normal postmenopausal range, ≤32.2 pg/mL), and 17-hydroxyprogesterone level (592 ng/dL; normal postmenopausal range, ≤45 ng/dL) (Table 1).

Pelvic ultrasound revealed a large, irregular, right adnexal mass measuring 14.7 × 9.7 × 12.3 cm, with Doppler-positive flow. The left ovary appeared normal. The endometrial thickness was increased at 9 mm, and calcifications were seen within the endometrium. In addition, a 1.4 cm × 1.5 cm × 1.1-cm, smooth mass was visualized within the myometrium, likely representing a myoma.

Ovarian cancer tumor markers were measured and the levels of the following markers were elevated: human epididymis protein 4 (210 pmol/L; reference range, 0-140 pmol/L), cancer antigen 125 (144 U/mL; reference range, 0-34 U/mL), and carcinoembryonic antigen (22.6 ng/mL; reference range, 0-5.0 ng/mL) (Table 2). α fetoprotein (and β human chorionic gonadotropin levels were not elevated (Table 2). Inhibin A level was elevated at 10.8 pg/mL (normal postmenopausal range, ≤6.9 pg/mL), while inhibin B level was not elevated (Table 2). The patient underwent targeted sequencing of 47 genes associated with cancers included in the Common Hereditary Cancers Panel (Invitae), which was negative for any germline disease-causing variants, including Lynch syndrome.

Computed tomography scanning with contrast of the chest, abdomen, and pelvis redemonstrated the large pelvic mass. No additional abnormalities were reported. The patient then underwent exploratory laparotomy with removal of the pelvic mass, total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, infragastric total omentectomy, and peritoneal, bladder, and bilateral paracolic gutter biopsies. Pathology showed an endometrioid adenocarcinoma with extensive squamous differentiation arising from the right ovary, International Federation of Gynecology and Obstetrics stage I, pT1aN0, 15.7 × 11.6 cm in size. Additional immunohistochemistry analysis of the carcinoma tissue showed positive staining for the steroidogenic enzymes side-chain cleavage enzyme, 17α-hydroxylase, and aromatase (Fig.). None of the other biopsied sites were involved by the carcinoma, and no malignant cells were identified in the peritoneal ascitic fluid or pelvic washings. The endometrium was noted to have complex atypical hyperplasia with secretory changes and contained a polyp. The myometrium contained adenomyosis and leiomyomata. Postoperative recovery was uneventful.

On postoperative day 11, the patient was feeling well and noted minimal vaginal spotting. Her estradiol and testosterone levels measured by enzyme-linked immunosorbent assay were undetectable (estradiol, <5 pg/mL; testosterone, <5 ng/dL). Due to the early stage of disease at the time of surgery and lack of evidence of metastases on all staging biopsies, the patient was followed without chemotherapy. In the year after surgery, regular pelvic examinations suggested no recurrence of the disease. Accordingly, ovarian tumor markers decreased to their normal ranges and remained stable 1 year after surgery (Table 2).

Discussion

Herein we describe a case of a testosterone-secreting endometrioid ovarian carcinoma in a postmenopausal woman presenting with hirsutism. Androgen excess in women can be the result of ovarian or adrenal androgen production. Initial investigation of the source of excess testosterone, in this case, was notable for a normal DHEA-S and unremarkable adrenal glands on a computed tomography scan. Further provocative testing was not done as the ovarian tumor was discovered and presumed to be the source of the hyperandrogenism.

Endometrioid ovarian carcinoma is a subtype of epithelial ovarian cancer, the most common type of malignant ovarian tumor.[1] The presenting symptoms of epithelial ovarian cancer often include mass effect and ascites,[12,13] while symptoms due to hormone secretion by these tumors are rare.[8,9] In contrast, ovarian

Table 1
Laboratory Test Results at Initial Evaluation

Test name	Reference range (postmenopausal)	Result
Testosterone (ng/dL)	2-45	282
Free testosterone (pg/dL)	0.2-5.0	19.7
Bioavailable testosterone (ng/dL)	0.5-8.5	38.8
Sex hormone binding globulin (nmol/L)	14-73	66
Albumin (g/dL)	3.5-5.2	4.3
Dehydroepiandrosterone sulfate (mcg/dL)	10-190	82
Estradiol (pg/mL)	≤32.2	72
17-Hydroxyprogesterone (ng/dL)	≤45	592
Creatinine (mg/dL)	0.5-1.1	0.81
Hemoglobin (g/dL)	11.5-16.0	15.3
Hematocrit (%)	34.0-47.0	44.1

Total testosterone was measured by liquid chromatography-mass spectrometry. Free testosterone was measured by equilibrium dialysis. Estradiol was measured by electrochemiluminescence immunoassay.

Table 2
Tumor marker measurements at diagnosis and postoperatively

Tumor marker	Reference range	Time of diagnosis	6 weeks after operation	1 year after operation
Human epididymis protein 4 (pmol/L)	0-140	210	60	52
Cancer antigen 125 (U/mL)	0-34	144	13	8
Carcinoembryonic antigen (ng/mL)	0.0-5.0	22.6		
α fetoprotein (ng/mL)	0.0-8.0	<1.3		
β human chorionic gonadotropin (mIU/mL)	0.0-4.9	<1.0		
Inhibin A (pg/mL)	≤6.9 (postmenopausal)	10.8		
Inhibin B (pg/mL)	≤16 (postmenopausal)	<10		

Human epididymis protein 4 and cancer antigen 125 were measured by electrochemiluminescence immunoassay. Carcinoembryonic antigen was measured by chemiluminescent immunoassay.

cancers derived from the sex cord and stroma, including granulosa and Leydig cell tumors, often do present with symptoms due to hormone production, such as virilization.[15]

An unusual property of the endometrioid ovarian cancer described in this case was its ability to produce testosterone, which led to pronounced symptoms of hyperandrogenism. This resulted in early diagnosis and, ultimately, successful treatment of this cancer. Immunohistochemistry of the carcinoma tissue revealed the expression of the key enzymes in the steroidogenic pathway (Fig.). Side-chain cleavage enzyme catalyzes the first step in the pathway using cholesterol as its substrate. 17α-hydroxylase is essential for the synthesis of androgens, such as testosterone, while aromatase converts androgens to estrogens. Elevated circulating levels of 17-hydroxyprogesterone, testosterone, and estradiol suggest that these enzymes were parts of a functional steroid-production mechanism within the tumor. The patient developed endometrial hyperplasia with secretory changes attributable to estrogen production by the tumor. Despite these changes, she did not experience vaginal bleeding. Endometrioid ovarian carcinoma is associated with cancer of the endometrium in 15% to 20% of cases.[6,19] In this case, the endometrium was not involved in the carcinoma.

It has been noted that some epithelial cell ovarian tumors can express steroid hormone receptors and be stimulated by increased steroid production in the adjacent benign stromal cells.[20] However, in the present case, it is clear that the steroidogenic enzymes are expressed in the tumor cells themselves, suggesting a different growth paradigm. While we did not assess the expression of hormone receptors in this tumor, it is possible that the steroid hormones produced by the tumor could have stimulated its growth in an autocrine manner.

The majority of published cases of endometrioid carcinomas do not report symptoms related to steroid hormone production by the tumors. This report adds to a small but growing number of published cases of testosterone-secreting endometrioid carcinomas arising in postmenopausal women. In 2001, Girsh et al[21] reported on a 62-year-old woman who presented with hypertension, polycythemia, hirsutism, and male pattern baldness. She was found to have a testosterone-producing endometrioid tumor of the ovary, and all of her presenting symptoms resolved after surgical resection of the tumor. This patient's testosterone level was much higher than in our case (28.5 nmol/L, or 822 ng/dL; reference range, 0.5-3.0 nmol/L), which likely explains the heightened severity of her symptoms.

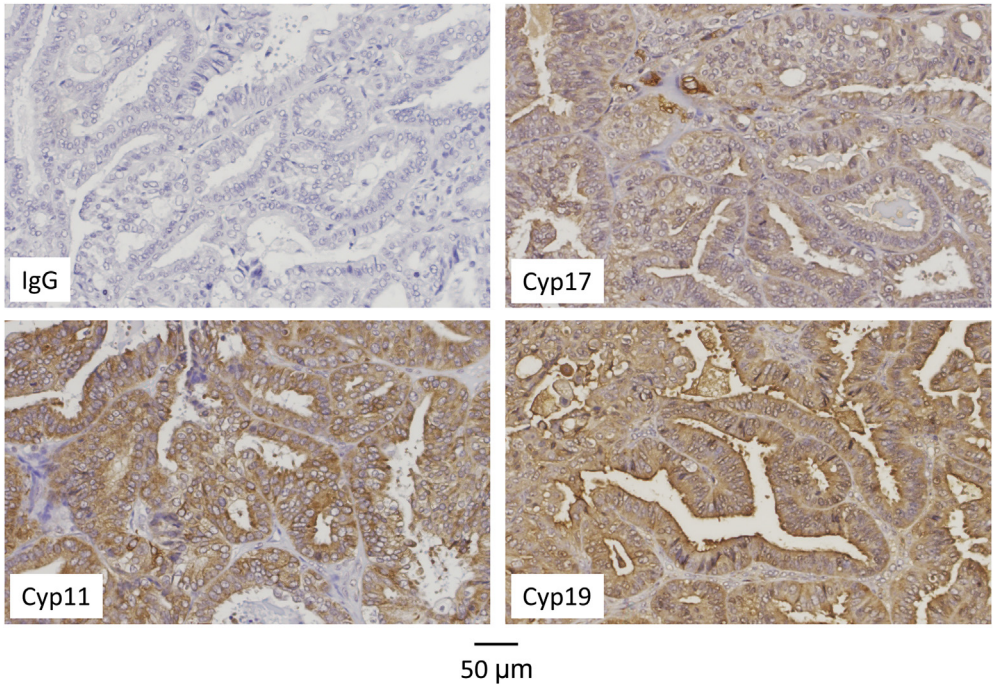

Fig. Expression of steroidogenic enzymes in the tumor tissue. Tissue sections were probed by immunohistochemistry after fixation in methanol. Primary rabbit antibodies against the indicated enzymes were obtained from Cell Signaling. Rabbit immunoglobulin (IgG) was used as the negative control. Biotinylated goat anti-rabbit secondary antibody (Vector Laboratories) was used in all experiments. Signal was developed using streptavidin-horseradish peroxidase (VECTASTAIN, Vector Laboratories). Cyp11 = side-chain cleavage enzyme; Cyp17 = 17α-hydroxylase; Cyp19 = aromatase.

Inhibins are granulosa- and Sertoli-cell-derived hormones that have been explored as potential tumor markers and prognostic indicators in ovarian cancer. Inhibins are usually elevated in sex cord and stromal cell cancers but may also be elevated in some epithelial ovarian cancers.[16-18] A possible correlation between steroid hormone and inhibin production by epithelial cell ovarian cancers has not been studied. In 2017, Shearer et al[22] reported a case of ovarian sertoliform endometrioid carcinoma discovered in a 70-year-old woman who presented with rapid virilization. This tumor notably produced inhibins. Similarly, in the case presented here, inhibin A was elevated, while inhibin B was normal (Table 2). It is, therefore, possible that inhibin production may be associated with steroid hormone production by ovarian tumors with endocrine features, such as sex cord and stromal cell cancers and the rare steroid-secreting epithelial cell cancers, although more studies are needed to test this hypothesis.

Conclusion

We present an unusual case of a postmenopausal woman presenting with symptoms of hyperandrogenism due to an endometrioid ovarian carcinoma. While sex hormone synthesis is very rare in epithelial cell cancers of the ovary, this tumor exhibited otherwise typical ovarian tumor markers. This case highlights the importance of timely investigation of symptoms of sex-steroid excess after menopause. Sex hormone secretion by epithelial cell ovarian carcinomas should be considered in cases of new-onset hyperandrogenism in postmenopausal women.

Data Availability

All data pertinent to this case is available upon request from the corresponding author.

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Disclosure

The authors have no multiplicity of interest to disclose.

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