Virilizing Leydig-Sertoli Cell Ovarian Tumor Associated with Endometrioid Carcinoma of the Endometrium in a Postmenopausal Patient: Case Report and General Considerations

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Abstract

Introduction: Sertoli-Leydig cell tumors (SLCTs) are rare tumors mostly occurring in young women. Here we report an unusual case of a SLCT with simultaneous occurrence of endometrioid adenocarcinoma of the endometrium in a woman in menopause.

Case report: A 67-year-old woman presented with progressive signs of virilization. Blood tests showed increased levels of testosterone, delta-4-androstenedione, and dehydroepiandrosterone (DHEA). DHEA-sulphate, 17β-estradiol, estrone, and sex-hormone binding globulin serum levels were within the normal range. Magnetic resonance imaging revealed a solid mass of $2.7 \times 2.9$ cm in the right ovary set against the background of the uterus. The patient underwent bilateral salpingo-oophorectomy with hysterectomy. The mass in the right ovary was a differentiated SLCT. Incidentally, the endometrium revealed an endometrioid adenocarcinoma. Following surgical treatment the plasma androgens dropped to normal levels, and signs and symptoms of virilization improved.

Conclusion: SLCT should be suspected in postmenopausal women who present rapid progressive androgen excess symptoms with hyperandrogenemia.

Keywords: ovarian cancer, hyperandrogenism, virilization, Sertoli-Leydig tumor, endometrial cancer
Introduction

Sertoli-Leydig cell tumors (SLCTs) are uncommon neoplasms, accounting for 1% of all sex cord-stromal tumors (0.1%-0.5% of all primary ovarian neoplasms). Some of these tumors are well differentiated, produce steroid hormones, and may be suspected in patients with estrogen-excess symptoms (precocious puberty, abnormal uterine bleeding, and endometrial hyperplasia or endometrioid carcinoma) or androgen-excess signs (hirsutism, virilism, acne, hyperseborrhea, and alopecia) associated with the presence of an ovarian mass. Benign, well-differentiated SLCTs often occur in young women with an average age of 25 years; less than 10% of the patients are over 50 years of age. They account for 10% of all SLCTs and are often associated with either congenital anomalies of internal genitalia or with testicular feminization syndrome. Microscopically, the tumors show uniform solid or tubular structures lined by Sertoli-type cells. Tubules may contain eosinophilic secretion. The intervening stroma contains a variable number of Leydig cells that tend to be packed in ribbons or nests between the tubules. Mitoses are rare. The neoplasm grading is an important predictive factor related to both prognosis and post-surgical follow-up of the patient. Here we report a rare case of simultaneous occurrence of SLCTs with endometrial carcinoma in a postmenopausal woman.

Clinical Case

A 67-year-old female was evaluated because of a progressive increase of hair growth of upper lip, chin, and linea alba, deepening of voice, increase in libido, mood instability, increment of muscle mass, and onset of frontal alopecia during the last six months. A transvaginal ultrasonography performed the previous year showed no abnormalities in her reproductive tract. She had two pregnancies, and menopause took place at the age of fifty. Her medical history included a total thyroidectomy for goiter and cholecystectomy in 2006, irritable bowel syndrome, and severe osteopenia treated with calcium (1000 mg daily) and ibandronate (150 mg once a month). Body weight was stable (body mass index, 30.4 kg/m²) and the blood pressure was normal (130/70 mmHg). On physical examination, a clitoromegaly, increased blood pressure was normal (130/70 mmHg). Body weight was stable (body mass index, 30.4 kg/m²) and the blood pressure was normal (130/70 mmHg). On physical examination, a clitoromegaly, increased

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During the reproductive age, the differential diagnosis of hyperandrogenemia includes polycystic ovary syndrome (PCOS), ovarian and adrenal androgen-secreting tumors, ovarian and adrenal steroidogenic enzyme deficiencies, as well as other endocrine disorders. In a postmenopausal woman, the main reason for a fast-developing hirsutism is cancer. The most common ovarian cancers related to hyperandrogenism are ovarian sex-cord stromal tumors, an extremely rare cause of virilization, comprising 5% to 8% of all primary ovarian neoplasm's. Rarely, SLCTs may be associated with hyperestrinism. An important aspect of our case report was the concomitant presence of SLCT and endometrioid adenocarcinoma of endometrium. Endometrial carcinomas are hormone-dependent tumors associated with high circulating levels of estrogens. The paradox consists in the evidence that endometrial carcinomas are a disease of aging with over 80% of cases occurring during menopause, a time during which estrogen secretion is waning. However, despite the decline of the ovarian function that follows menopause, estrogen synthesis continues during the postmenopausal years through increases of estrone formation from androgens of adrenal and ovarian origin. The reaction that takes place in the adipose tissue and enhances with body weight and advanced age may produce high concentrations of estrogens. Despite the high levels of androgens, we did not find high levels of estrogens in

Figure 1. Microscopy and immunohistochemistry of the SLCT of the right ovary (A–C) and histology of the endometrioid carcinoma of the endometrium (D). (A) Tubular structures lined by Sertoli-type cells with variable number of Leydig cells packed in ribbons or nests between tubules (H and E, ×40). (B) Positivity for inhibin of both Sertoli and Leydig cells components of the SLCT (H and E, ×40). (C) Positivity for pancitokeratine (H and E, ×40). (D) histological appearance of the endometrial neoplasm (H and E, ×40).

Figure 2. Effect of salpingo-oophorectomy with hysterectomy on alopecia and hair growth on linea alba. (A) Scalp of the patient before surgery. (B) Scalp of the patient 12 months after surgery. (C) Videodermoscopy of the linea alba before surgery. (D) Videodermoscopy of the linea alba 12 months after surgery. Note: Red dots indicate hair follicles.

Discussion

Here we report a case of SLCT associated with endometrial carcinoma in a postmenopausal woman with hyperandrogenism. During the reproductive age, the differential diagnosis of hyperandrogenemia includes polycystic ovary syndrome (PCOS), ovarian and adrenal androgen-secreting tumors, ovarian and adrenal steroidogenic enzyme deficiencies, as well as other endocrine disorders. In a postmenopausal woman, the main reason for a fast-developing hirsutism is cancer. The most common ovarian cancers related to hyperandrogenism are ovarian sex-cord stromal tumors, an extremely rare cause of virilization, comprising 5% to 8% of all primary ovarian neoplasm's. Rarely, SLCTs may be associated with hyperestrinism.

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our patient. However, a role of hyperandrogenemia as a risk condition for endometrial cancer development must be considered. Androgens are involved in many regulatory processes in the endometrial epithelia.13 The androgen receptor has been found both in normal endometrium, endometrial hyperplasia, and endometrial adenocarcinoma, and DHT plays an important role in the regulation of androgen action in endometrial cancer and normal human endometrium.14 Furthermore, a local endometrial conversion of androgens to estrogens due to the high endometrial aromatase P450 expression15 cannot be excluded.

An alternative and intriguing explanation for the concomitant development of SLCT and uterine tumor in our patient could be provided by mutations of the STK11/LKB1 gene at chromosome 19p13.3. Germline STK11 gene mutation is the underlying genetic alteration responsible for most cases of Peutz-Jeghers’s syndrome (PJS).16,17 A rare autosomal dominant disorder characterized by mucocutaneous pigmentation, hamartomatous polyposis, and predisposition to benign and malignant tumors of the gastrointestinal tract, breast, ovary, uterus, and testis.18 Women with PJS have an increased incidence of SLCT and adenocarcinoma of the uterine cervix,19 but STK11/LKB1 gene mutations may drive human endometrial carcinogenesis as well.20,21 Since allelic losses at chromosome region 19p13.3 occur in at least a subset of sporadic cases of SLCT,19 this has generated substantial interest in evaluating sporadic cancers of the same type as those observed in PJS patients for mutations in this gene. Thus, a potential role of a mutation in the STK11/LKB1 gene in our patient cannot be ruled out.

In conclusion, SLCTs are rare functionally active ovarian neoplasms, which must be suspected in postmenopausal women who present rapid progressive androgen excess symptoms and virilization with hyperandrogenemia. The concomitant presence of endometrial carcinoma despite the normal circulating levels of estrogens suggests a direct androgen action on the endometrium. Accordingly, endometrial cancer risk among postmenopausal women was positively associated with increasing levels of testosterone.22 However, a local conversion of excess androgens to estrogens as potential stimulants of endometrium proliferative activity cannot be ruled out. To the best of our knowledge, this is the first report23 describing the hormonal status in a postmenopausal woman affected by this rare condition.

Author Contributions
Conceived and designed the experiments: PDG, AF, LG, CM. Analyzed the data: PDG, LC, GV, LG, EC, LG, CM. Wrote the first draft of the manuscript: SM, AF, LG, CM. Contributed to the writing of the manuscript: LG, CM. Agree with manuscript results and conclusions: PDG, LC, GV, LG, EC, SU, SM, CA, AF, LG, CM. Jointly developed the structure and arguments for the paper: LG, CM. Made critical revisions and approved final version: LG, CM. All authors reviewed and approved of the final manuscript.

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