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An Ovarian Steroid Cell Tumor Causing Virilization and Massive Ascites

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Steroid cell tumors, not otherwise specified (NOS), are rare ovarian sex cord-stromal tumors with malignant potential. The majority of these tumors produce several steroids, particularly testosterone. Various virilizing symptoms such as hirsutism, temporal balding, and amenorrhea are common in these patients; however massive ascites is an infrequent symptom. A 52-year-old woman with the sudden onset of virilization and massive ascites presented for treatment at Severance Hospital. After clinical evaluation, the patient underwent an exploratory laparotomy and a complete surgical staging procedure. She recovered from the surgery uneventfully and was discharged from the hospital five days after surgery. We present here an unusual case of an ovarian steroid cell tumor, NOS, and a brief review of the literature regarding these types of tumors.

Key Words: Ascites, hirsutism, virilization, tumors, ovary

INTRODUCTION

Ovarian steroid cell tumors are very rare sex-cord stromal tumors comprising less than 0.1% of all ovarian tumors. A subtype of this tumor type, called not otherwise specified (NOS) accounts for approximately one-half of all ovarian steroid cell tumors. Approximately one-third of steroid cell tumors in adults have been reported to be malignant.[1] Because steroid cell tumors secrete testosterone and other steroid hormones, these tumors may cause precocious puberty in children and virilization in adults.[1-4] Patients with NOS tumors can present with symptoms of pain, abdominal distention, and bloating; however, ascites is an uncommon symptom.[5]

In an extensive literature search of the MEDLINE database from 1979 to the present, only 74 cases of ovarian steroid cell tumors were identified. Previously, such tumors were designated as lipid or lipoid cell tumors of the ovary.[6,7]

Because ovarian stromal tumors occur so infrequently, little attention has been given to their response to therapies such as surgery, chemotherapy, or radiation. A recent report stated gonadotropin releasing hormone agonist was effective in treating steroid cell tumors.[8,9] Here, we present the case of a patient with a rare NOS steroid cell tumor who exhibited massive ascites and virilization, and had a complete and dramatic response to surgery which was her only treatment.

CASE REPORT

A 52-year-old, gravida 2, para 2 female presented for treatment at Severance Hospital with a 4 month history of increasing abdominal distention, weight gain, and hirsutism. This patient had menarche when she was 13 years old and had a vaginal hysterectomy 10 years ago to remove fibroids. She had not taken any hormones, special drugs, or had any additional surgeries. In addition, there was nothing notable in her family

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history.

At presentation, she was plethoric with facial roundness, had thin and greasy skin, a blood pressure of 110/70 mmHg, and severe facial hair growth that required daily chin and lip shaving, She did not have any muscle weakness, back pain, bruising, striae, or acne. Eczematous dermatitis was detected on both breasts. Her abdomen was very distended with ascites. Percussion did not reveal locomotive dullness. A pelvic examination revealed an enlarged clitoris and left adnexal fullness.

A transvaginal ultrasound identified a 5.5 × 7.2 cm, solid, left ovarian tumor with massive ascites. Morphologic indexing of this tumor was performed according to the Sassone scoring system[10] and showed a potential for malignancy (score = 9). A computed tomography (CT) pelvic scan confirmed the ultrasound findings and detected no adrenal gland enlargement or additional tumors. An analysis of the ascites aspiration revealed macrophages and lymphocytes, but no malignant cells. Laboratory evaluations showed a normal blood cell count, electrolyte level, and hepatorenal profile. In addition, hormone profiles demonstrated normal values for serum prolactin, cortisol, thyroid-stimulating hormone, 17α-hydroxypregnenolone, and human chorionic gonadotropin. Furthermore, the patient had a serum follicle-stimulating hormone level of 1.1 mIU/mL (postmenopause > 30 mIU/mL), a serum testosterone level of 1.9 ng/mL (normal 0.4-0.76 ng/mL), and a serum dihydroepiandrosterone sulfate (DHEA-S) level of 78 μg/dL (normal 35-430 μg/dL). Tumor markers, including carcinoembryonic antigen (CEA), CA 19-9, CA 15-3, and α-fetoprotein (AFP) were also normal. In contrast, her serum CA 125 level was above normal (362.4 U/mL).

The patient underwent exploratory laparotomy. During the laparotomy, 6.5 L of straw-colored ascitic fluid was evacuated and was found to be negative for malignancy. The enlarged left ovary was smooth, had no external excrescences, and measured 5.5 × 7.5 × 4.5 cm (Fig. 1). The right ovary and all peritoneal surfaces were normal. A frozen section of the left ovary was classified as a stromal tumor of unknown malignant potential. A complete surgical staging procedure was performed including: bilateral salpingo-oophorectomy, infracolic omentectomy, multiple peritoneal biopsies, and pelvic-paraaortic lymph node sampling. Microscopically, the tumor was characterized by nodular masses of cells with variable appearance. In some areas, the cells contained abundant eosinophilic cytoplasm, and in other areas the cytoplasm had a foamy feature consistent with the appearance of lipids. No Reinke crystals were noted. There was also no significant

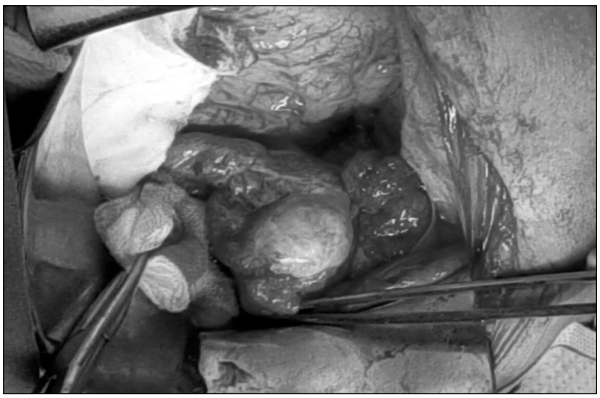

Fig. 1. The enlarged left ovary was smooth, had no external excrescences, and measured 5.5 × 7.5 × 4.5 cm.

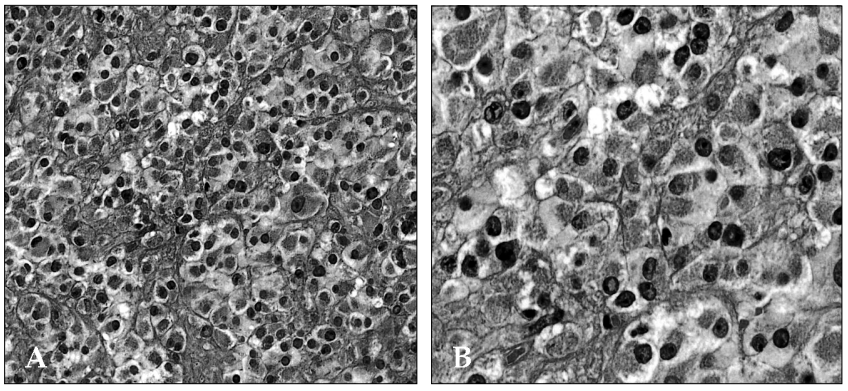

Fig. 2. Microscopic findings. (A) The cells show abundant eosinophilic cytoplasm and no crystals of Reinke (H&E staining, 100 × original magnification). (B) Tumor cells demonstrate a diffusely vacuolated cytoplasm (H&E staining, 400 × original magnification).

necrosis, mitotic activity, or high-grade nuclear atypia (Fig. 2). These features were consistent with a benign ovarian steroid cell tumor NOS.

The patient recovered from the surgery uneventfully and was discharged from the hospital five days after surgery. At the time of her first postoperative visit to the outpatient clinic 3 weeks after surgery, her virilization and hirsutism were improved and her serum CA 125 level had decreased to 31.98 U/mL. In addition, her hormone levels were within the normal range: testosterone, 0.2 ng/mL, DHEA-S, 73 μg/dL, and androstenedione, 2.5 ng/mL (normal range, 1.1-3.9 ng/mL). Furthermore, her 24-hour urine 17-ketosteroid value was 7.1 mg/day (normal range, 6-15 mg/day). She currently remains entirely asymptomatic 2 years after surgery.

DISCUSSION

Ovarian steroid cell tumors have been classified in three subtypes: NOS, Leydig cell, and stromal luteoma. NOS steroid cell tumors are comprised of two types of polygonal cells that differ only in their cytoplasmic appearance (eosinophilic vs. vacuolated). The originating cells of the tumor may be derived from adrenal rest cells, ovarian-stromal lutein cells, or Leydig cells.[1,2] NOS steroid cell tumors are differentiated from Leydig cell tumors because of their lack of cytoplasmic Reinke crystals. The histopathological term "steroid cell tumors of the ovary" was first described by Scully.[2] Prior to Scully's description, these tumors were classified as lipid or lipoid cell tumors.[6,7] Such terminology was obscure because some tumors have little or no lipid present.[1-3]

NOS tumors can occur at any age, but usually develop in adults with an average age of 43 years. The major symptoms detected in 56-77% of patients are hirsutism and virilization.[2,3] Reedy et al. reported a case of an undifferentiated NOS steroid cell tumor with hirsutism, amenorrhea, clitoromegaly, and temporal baldness.[11] We also detected hirsutism, and other virilization symptoms in our patient. Although abdominal distention and bloating can present in steroid cell tumors, massive ascites and elevated CA125 levels are infrequent.[5] Outwater et al. reported that virilizing ovarian tumors are not associated with the ascites. The unique features of our case were that the patient had symptomatic massive ascites and elevated CA 125 levels. Conjecturally, in our patient, the steroid cell tumor and its ascites mechanically irritated the mesothelium causing overexpression of CA 125. Estradiol secretion has been detected in 6-23% of patients. In these patients, menorrhagia and the irregular bleeding after menopause were detected.[2,3] Luk et al. reported a steroid cell tumor case that was associated with inner membrane glandular tumors of the uterus.[12] In addition, Cushing' syndrome has been reported in steroid cell tumor patients due to plasma prorenin and hypokalemia levels.[6,13,14]

NOS steroid cell tumors, can present in patients as abdominal distention and bloating. However, the most interesting cases are those involving sex hormonal activity and virilizing tumor characteristics. In virilized patients, serum testosterone levels of more than 2.0 ng/mL, normal DHEA-S levels, and no evidence of 21α-hydroxylase deficiency are strong indicators of the presence of an ovarian virilizing tumor or ovarian hyperthecosis. To rule out late onset congenital adrenal hyperplasia in young women, assessment of plasma 17α-hydroxyprogesterone levels was recommended.[1] In addition, the technique of radiolabeled ^{131}I-aldosterol, ^{131}I-iodocholesterol, and ^{75}Se-selenomethycholesterol imaging analysis has been reported.[15,16] NOS tumors must be distinguished from other steroid cell tumor types which include: luteinized thecomas, pregnancy luteomas and carcinomas, primary clear cell carcinoma, and metastatic renal cell carcinoma. Identifying both hilus cell tumors and rare non-hilar type Leydig cell tumors with certainty requires demonstrating the cytoplasmic presence of Reinke crystals in the neoplastic cells.[2] In this study, our patient presented with a serum testosterone level of 1.9 ng/mL (normal range, 0.4-0.76 ng/mL). Her serum DHEA-S and 17α-hydroxypregnenolone levels were 78 μg/dL (normal range, 35-430 μg/dL) and 1.6 ng/mL (normal range, 0.1-4.0 ng/mL), respectively.

A study by Hayes and Scully reported the most predictive malignant features of ovarian steroid cell tumors.[2] According to their criteria, the most accurate predictor of malignant behavior in these

tumors is the presence of two or more mitotic figures per 10 high-power fields. In addition, the majority of malignant tumors also demonstrate grade 2-3 nuclear atypia, necrosis, hemorrhage, and a tumor diameter greater than 7 cm. Most tumors are unilateral (94%) and the majority are capable of sex steroid hormone production. In adults, approximately a quarter of steroid cell tumors are malignant.

The mainstay of ovarian steroid cell tumor treatment is surgery. Surgical treatments using total abdominal hysterectomy, bilateral salpingo-oophorectomy, and complete surgical staging are an appropriate management option for old women who do not want to preserve their fertility, as was our case. However, in young patients, unilateral salpingo-oophorectomy is adequate most of the time due to the low bilateral frequency of 6%. However such practices require a mandatory follow-up evaluation and should include a measurement of sex hormone levels, particularly for those patients who demonstrated elevated levels before removal of the primary tumor. Additionally, a gonadotropin releasing hormone agonist could be used as postoperative adjuvant therapy.[8,9] In adults, approximately 25-43% of steroid cell tumors are malignant.[2,4] Patients with large ovarian tumors and advanced stage disease had a worse prognosis than those with early stage steroid cell tumors.[2] Malignant NOS steroid cell tumors should be managed with surgical removal followed by combination chemotherapy. The therapeutic value of chemotherapy and radiotherapy in the treatment of NOS tumors is poorly understood as most of these tumors are diagnosed in an early stage and do not recur or metastasize.

Ovarian NOS steroid cell tumors, are very rare tumors that can be difficult to diagnose. These tumors should be considered in the differential diagnosis of isosexual precocious puberty in children and virilization in adults. Disease management should be individualized based on tumor pathology, surgical staging, and the desire for preserving fertility.

We report here a NOS steroid cell tumor in a patient with massive ascites and a markedly elevated plasma CA125 level. The patient underwent surgical treatment and our current patient follow-ups have not detected any residual tumors or recurrences.

REFERENCES

1. Scully RE. Tumors of the ovary and maldeveloped gonads, fallopian tuge, and broad ligament. In: Atlas of Tumor Pathology. 2nd ed. Washington, DC: Armed Forces Institute of Pathology; 1979. p.215-20.
2. Hayes MC, Scully RE. Ovarian steroid cell tumors (not otherwise specified). Am J Surg Pathol 1987;11:835-45.
3. Hartman LC, Young RH, Evans MP, Podratz KC. Ovarian sex cord-stromal tumors. In: Hoskins WJ, Perez CA, Young RC, editors. Principles and Practice of Gynecologic Oncology. 2nd ed. Philadelphia: Lippincott-Raven; 1997. p.1015-9.
4. Wang PH, Chao HT, Lee RC, Lai CR, Lee WL, Kwok CF, et al. Steroid cell tumors of the ovary: clinical, ultrasonic, and MRI diagnosis--a case report. Eur J Radiol 1998;26:269-73.
5. Outwater EK, Marchetto B, Wagner BJ. Virilizing tumors of the ovary: imaging features. Ultrasound Obstet Gynecol 2000;15:365-71.
6. Tayler HB, Norris HJ. Lipoid cell tumors of the ovary. Cancer 1967;20:1953-62.
7. Donovan JT, Otis CN, Powell JL, Cathcart HK. Cushing's syndrome secondary to malignant lipoid cell tumor of the ovary. Gynecol Oncol 1993;50:249-53.
8. Brewer CA, Shevlin D. Encouraging response of an advanced steroid-cell tumor to GnRH agonist therapy. Obstet Gynecol 1998;92(4 Pt 2):661-3.
9. Wang PH, Chao HT, Lee WL. Use of a long-acting gonadotropin-releasing hormone agonist for treatment of steroid cell tumors of the ovary. Fertil Steril 1998;69: 353-5.
10. Sassone AM, Timor-Tritsch IE, Artner A, Westhoff C, Warren WB. Transvaginal sonographic characterization of ovarian disease: evaluation of a new scoring system to predict ovarian malignancy. Obstet Gynecol 1991; 78:70-6.
11. Reedy MB, Richards WE, Ueland F, Uy K, Lee EY, Bryant C, et al. Ovarian steroid cell tumors, not otherwise specified: a case report and literature review. Gynecol Oncol 1999;75:293-7.
12. Luk WT, Lee N, Chang TC, Chu KK. Lipid cell tumor of the ovary associated with endometrial adenocarcinoma-a case report. Changgeng Yi Xue Za Zhi 1989;12:244-8.
13. Elhadd TA, Connolly V, Cruickshank D, Kelly WF. An ovarian lipid cell tumour causing virilization and Cushing's syndrome. Clin Endocrinol 1996;44:723-5.
14. Anderson PW, d'Ablaing G 3rd, Penny R, Sherrod A, Do YS. Secretion of prorenin by virilizing ovarian tumor. Gynecol Oncol 1992;45:58-61.
15. DeFreitas EA, Dudzinski MR, LaRocque JC, Coddington CC. Ovarian vein sampling in rapidly progressing

virilization. A case report. J Reprod Med 1991;36:546-8.
16. Younis JS, Bercovici B, Zlotogorski A, Horne T, Glaser B. Lipid cell tumor of the ovary: steroid hormone secretory pattern and localization using ^{75}Se-selenomethylcholesterol. Gynecol Obstet Invest 1989;27:110-2.