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Sertoli-Leydig cell tumor characterized by hyperestrogenism in a postmenopausal woman: a case report and review of the literature

L. Wang[1,2,3,4], A. Yao[1], A. Zhang[1], P. Qu[5]

[1]The Third Central Clinical College of Tianjin Medical University, Tianjin; [2]Tianjin Key Laboratory of Artificial Cell
[3]Artificial Cell Engineering Technology Research Center of Public Health Ministry, Tianjin
[4]Tianjin Institute of Hepatobiliary Disease, Tianjin; [5]Tianjin Central Hospital of Gynecology and Obstetrics, Tianjin (China)

Summary

Sertoli-Leydig cell tumor (SLCT) is a rare neoplasm from the group of sex-stromal tumors of ovary, which accounts for < 0.5% of all primary ovarian tumors. The tumor can occur in all ages but is more often seen in young women at the mean age of 25 years. Less than 10% of the SLCTs occur before menarche or after menopause. Although most SLCTs have a good prognosis if detected in Stage I, but the most common are those with moderate or poor differentiation. In order to monitor the risk of disease recurrence, close follow-up is required. In this article the rare case of SLCT in a 62-year-old woman characterized by postmenopausal bleeding and hyperestrogenism was reported, The clinical and pathological characteristics were described. Clinicians should consider that patients with postmenopausal bleeding and hyperestrogenism should be highly suspicious of SLCT, and more prospective studies on the diagnosis and the course of the diseases are needed.

Key words: Sertoli-Leydig cell tumor; Hyperestrogenism; Postmenopausal bleeding.

Introduction

Sertoli-Leydig cell tumor (SLCT) of ovary, also known as androblastoma, is a rare neoplasm from the group of sex -stromal tumors of ovary. This tumor accounts for < 0.5% of all primary ovarian tumors [1]. The tumors occur in all age groups but are more often seen in young women at an average age of 25 years [2, 3]. Less than 10% of the SLCTs occur either prior to menarche or after menopause [1]. About nearly half of the patients have no endocrine symptoms, and more than one-third of these patients develop signs of virilization, such as increasing facial hair, deepening of the voice, a blunt pain of the abdomen and enlargement of the clitoris, by hormonal hyperproduction of testosterone, but they rarely present manifestations of hyperestrogenism. The clinical characteristics of SLCT are reported to be associated to the degree of histological differentiation. SLCTs are grouped into well-differentiated, intermediately differentiated, and poorly differentiated, and the degree of differentiation determines the prognosis of patients [4]. In well differentiated tumors, the malignant potential is zero, 11% in the intermediate type, 59% in the poorly differentiated tumors, and 19% of them contain heterologous components[5]. Because of the low incidence of the disease and fewer reports, the management of SLCT is still a challenge [6]. The following case describes a postmenopausal woman with a Sertoli-Leydig ovarian tumor with postmenopausal vaginal bleeding and hyperestrogenism that received radical surgery. A review of the relevant literature was additionally conducted.

Case Report

Ethical approval was given by the medical ethics committee. A 62-year-old woman, G3P2, had her last menstrual period at the age of 52. She had irregular postmenopausal bleeding three times in the past two years, and the amount of bleeding was less than normal menstruation. Ultrasound (July 18, 2015): endometrial thickness was 7 mm. Then the patient underwent a hysteroscopy and no abnormalities were detected. The patient was followed up until October in 2016; she had vaginal bleeding one more time. The patient was admitted to this hospital and ultrasound revealed a thickened endometrium, which was 10 mm, without enlargement of ovaries. Laboratory examination revealed an elevated estradiol value of 55.30 pg/mL, a suppressed follicle-stimulating hormone (FSH) level of 14.10 IU/L, and a luteinizing hormone (LH) level of 8.70 IU/L. The hormonal profile of the case also included normal thyrotropin and progesterone in serum. Tumor markers, including CA125, CA199, alpha-fetoprotein (AFP), and carcinoembryonic antigen (CEA) were all within normal limits (Table 1). Then the patient underwent another hysteroscopy and no abnormalities were still not detected. A diagnostic laparoscopy was performed, with the finding of a 3×2×2 cm right ovarian mass, the uterus and left ovary appeared normal. Bilateral oophorectomy, combined with hysterectomy was performed. Pathological analysis confirmed a high degree differentiated

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Table 1. — *Tumor markers compared \ pre-operatively and post-operatively.*

	Pre-operative	Post-operative
CA199 (U/mL)	20.96	19.73
CA724 (U/mL)	0.97	0.98
CEA (ng/mL)	2.39	1.95
CA125 (U/mL)	16.25	20.26
CA153 (U/mL)	8.88	8.42

SLCT of the right ovary, with heterologous components (Figure 1). No areas of malignant transformation were identified on multiple sections of the surgical specimen. Immunohistochemical analysis showed a positive stain for inhibin-alpha, Ki-67, local-cytokeratin, and progesterone receptor (PR), whereas estrogen receptor (ER), epithelial membrane antigen (EMA), and p63 were negative. Adjuvant chemotherapy was recommended and the serum values of sex hormones (Table 2) were monitored. Laboratory examination revealed estradiol value decreased significantly compared with preoperative. Furthermore, serum testosterone value reduced from 43.40 ng/dl to less than 20 ng/dl after surgery. It was Stage IA according to FIGO 2009 staging system for ovarian cancer, and the patient remains under follow-up and there is no evidence of recurrent disease.

Discussion

SLCT belongs to the group of sex cord-stromal tumor (SCST) of the ovary, which is usually unilateral. Young women with SLCT usually present virilization, but the postmenopausal patients do not. SLCT can be inactive but elevated serum testosterone level is found in about 80% of patients. More rarely estrogen excess can be seen [7]. In postmenopausal patients, excess estrogen may be associated with SLCT, although most patients do not have endocrine symptoms or masculinization.

In the present case, the main clinical feature was postmenopausal hemorrhage, indicating hyperestrogen in the patient. Hormone assays showed high serum estradiol values and suppressed FSH and LH, which were associated with the hyperestrogenic symptoms. Then the hormone assays showed an unsuppressed FSH level of 87.4 IU/L and a LH level of 30.6 IU/L two months after surgery. Furthermore, serum testosterone and prolactin values decreased. The literatures on SLCT in postmenopausal women were reviewed; Young *et al.* [7] described that 5.6% (2/38) patients presented postmenopausal bleeding in patients with SLCT containing heterologous elements in the form of gastrointestinal-type epithelium, whereas Demidov *et al.* [7] reported that three cases of SLCT patients had postmenopausal bleeding. However, they had not monitored a hormone profile to ensure whether the symptoms were caused by elevated estrogen levels. In this case, the present authors compared the hormone profiles preoperatively and postoperatively, and they indicated that SLCT could raise serum estradiol and testosterone values, while FSH and LH were suppressed.

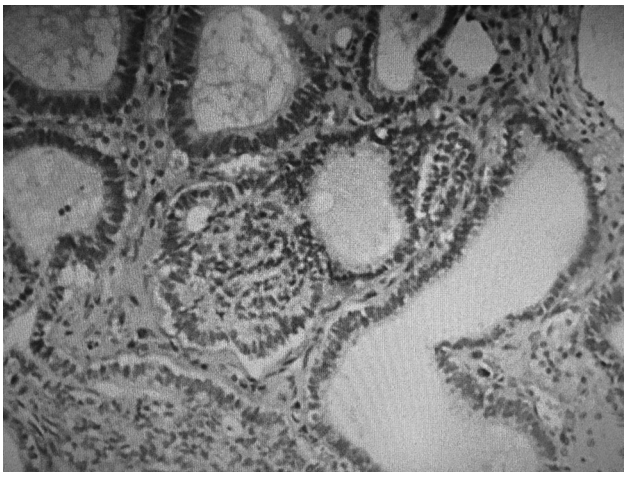

Figure 1. — Histopathological image of the ovary with a Sertoli-Leydig cell tumor. Hematoxylin and Eosin staining (×200).

Immunohistochemically, SLCT is positive for inhibin, which was consistent with the present immunological findings. In addition, the diagnosis of SCST was supported by a positive staining for inhibin-a and negative staining for EMA [8]. The negative results of ER and PR were reported to be a beneficial addition to the traditional immunohistochemical markers, such as inhibin, EMA, CD99, and pan-CK, to distinguish Sertoli cell tumor and endometrial tumor [9]. In the present case, PR was positive and 13% of Sertoli cells were reported to be positive.

In histology, SLCTs are classified (WHO) as 1) well-differentiated (11%), 2) intermediately differentiated (54%), 3) poorly differentiated (13%), 4) with heterologous composition (22%), and 5) retiform type (15%) [6, 10-12]. Well differentiated tumor cells were arranged in a tubular arrangement by Sertoli cells, which were separated by different Leydig cells. The intermediate type is characterized by cords, sheets, and aggregates of Sertoli-like cells separated by spindle stromal cells and recognizable Leydig cells. Poorly differentiated tumours show masses of spindle-shaped cells arranged in a sarcomatoid pattern [13]. SLCT associated with heterologous elements are composed of two kinds of components: one has endodermal elements from gastric and intestinal mucin secreting epithelium, and the other one has mesenchymal elements which present immature cartilage or skeletal muscle [13, 14]. There was a significant correlation between the prognosis of SLCTs and tumors' grade and stage [6, 10, 11, 15]. Metastasis is usually found in lungs, scalp, lymph nodes, and liver [11]. In the present case, a 62-year-old female had a right ovarian SLCT of well differentiation and in Stage IA, which contained heterologous elements. No metastasis was found in this case.

Ultrasonography is recommended as the first choice for gynecological tumor examination, while histopathological examination is still the gold standard of diagnosis. Twenty

Table 2. — *Serum levels of sex hormones compared pre-operatively and post-operatively.*

	Pre-operative	Post-operative			
	2016-12-4	2016-12-22	2017-1-18	2017-2-8	Reference
Prolactin (ng/ml)	10.40	5.95	5.26	7.13	1.9-25
Testosterone (ng/dl)	43.40	< 20	< 20	< 20	0-73
Progesterone (ng/ml)	0.24	< 0.20	0.30	< 0.20	< 1.00
Estradiol(pg/ml)	55.30	43.70	35.80	37.80	0-30
LH (IU/L)	8.70	10.60	30.20	30.60	11.30-39.80
FSH (IU/L)	14.10	36.20	83.40	87.40	21.70-153

percent of SLCTs are small size of ovary. It was only 3×2×2 cm in this case, which is not recognized by ultrasonography, hence the accurate diagnosis and positioning is challenging [16]. When patients with abnormal hormone levels in serum, but imaging examination does not find the mass and tumor markers are negative, as in the present case, it may be misdiagnosed as non-malignant diseases. Conservative observations should be cautious as it may delay necessary surgical detection. In addition, in the treatment of SLCT patients with secondary amenorrhea, with or without virilization, serum androgen level shall be measured in the process of diagnosis, such as in certain cases, the serum testosterone level may be the only preoperative pointing of an SLCT. Differential diagnosis of other causes with hyperandrogenemia (Cushing's syndrome, pituitary tumors, or hyperandrogen secretion) should be performed [17].

Well-differentiated SLCTs typically present with benign behavior [16]. Malignancy is observed in 11% of intermediately differentiated and 59% of poorly differentiated SLCTs. In addition, the five-year overall survival rate is almost 92% in cases of Stage I diseases [18]. The main treatment of SLCT is surgery on the basis of patient age, disease stage and tumor grade [19]. However, an important problem in patients of age is the retention of fertility (which is retained by cystectomy or adnexectomy except other female genital tracts). Hysterectomy accompanied by bilateral salpingo-oophorectomy, but also staging surgery (cytology, omentectomy, pelvic-para-aortic lymphadenectomy or peritoneal biopsies), is the most ideal treatment for patients after reproductive age; even then the necessity of lymph node resection remains debatable [18]. Brown e*t al.* [20] showed that lymph node metastasis is significantly decreased in SLCTs, therefore sampling of retroperitoneal nodes could be left out. Chemotherapy can be performed after surgery, especially for poorly performing or intermediately differentiated tumors [16]. In the present case, a postmenopausal patient having SLCT containing heterologous elements of well-differentiation and Stage IA at presentation underwent hysterectomy accompanied by bilateral salpingo-oophorectomy and postoperative chemotherapy.

In conclusion, though SLCT of ovary most commonly present with androgenic manifestations, rarely it can also present with estrogenic manifestations as in the present case. Therefore, whether an abdominal mass is found or not, postmenopausal hemorrhage with hyperestrogenism should be thoroughly investigated, keeping SLCT in mind which has good prognosis if detected in Stage I.

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Corresponding Author:
PENGPENG QU, M.D.
Department of Gynecological Oncology
Tianjin Central Hospital of Gynecology and Obstetrics
156 Nankai Third Road, Nankai
Tianjin 300100 (China)
e-mail: qu.pengpeng@hotmail.com