

## Case Report

## Sertoli–Leydig cell tumor presenting hyperestrogenism in a postmenopausal woman: A case report and review of the literature

Lili Guo<sup>a</sup>, Xiang Yang<sup>b</sup>, Huiting Zhu<sup>a</sup>, Weimin Qiu<sup>a</sup>, Xiaofei Shi<sup>a</sup>, Bingqing Huang<sup>a</sup>,  
Tao Duan<sup>a,\*</sup><sup>a</sup> Shanghai First Maternity and Infant Hospital, Tongji University, School of Medicine, Shanghai, China<sup>b</sup> Department of Obstetrics and Gynecology, Shanghai Tongji Hospital, Tongji University, School of Medicine, Shanghai, China

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## Abstract

**Objective:** Sertoli–Leydig cell tumor (SLCT) accounts for <0.5% of all ovarian tumors, which is unusual in postmenopausal women. Postmenopausal women with SLCT usually become virilized. We report a postmenopausal woman with SLCT presenting with hyperestrogenism.

**Case Report:** We report a rare case of SLCT in a postmenopausal woman aged 61 years, who presented with postmenopausal bleeding, endometrial hyperplasia and mucous polyp, elevated estradiol, and decreased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) values, all suggesting hyperestrogenism. Transvaginal ultrasound revealed several small cyst locules, detected inside the right ovary, with a maximum diameter of 7 mm. The diagnosis was delayed because of the atypical clinical manifestation and negative serum tumor markers. The frozen section investigation revealed SLCT intraoperatively, which was confirmed by histopathological and immunocytochemical examination. The tumor was positive for inhibin- $\alpha$ , pancytokeratin, and p53 and in isolated tumor cells, positive for Ki-67.

**Conclusion:** This case of SLCT suggests the existence of a new specific type of endocrine complex disease.

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**Keywords:** hyperestrogenism; postmenopausal bleeding; postmenopausal woman; Sertoli–Leydig cell tumor

## Introduction

Sertoli–Leydig cell tumor (SLCT) belongs to the group of sex cord-stromal tumors (SCST) of the ovary, which accounts for <0.5% of all ovarian tumors [1]. Approximately three-quarters of these tumors occur at the age of 20–30 years and <10% occur either prior to menarche or after menopause [2], although the youngest case was reported to be 12 months old [3]. The clinical characteristics of SLCT are reported to be associated to the degree of histological differentiation [4]. SLCT is usually associated with virilization [5]; association with hyperestrogenism is very rare in postmenopausal women. We present a case of SLCT with symptoms associated with

increased estrogen levels, instead of virilization, in a postmenopausal woman. We believe that our case is a useful addition to the literature.

## Case report

A 61-year-old woman, G<sub>2</sub>P<sub>1</sub>, had her last menstrual period at the age of 55, but presented with regular postmenopausal bleeding 1 year ago. She experienced each postmenopausal bleeding for approximately 1 week every month, which was similar to normal menstruation. The patient underwent hysteroscopy for postmenopausal bleeding; an endometrial polyp was removed and histological examination revealed the simple endometrial hyperplasia. The patient was administered oral norethisterone and monitored by pelvic ultrasound monthly, which showed the development of a progressively thickened endometrium and a slightly enlarged right ovary measuring

\* Corresponding author. Changle Road, 536, Shanghai 200040, China.  
E-mail address: [tduan@yahoo.com](mailto:tduan@yahoo.com) (T. Duan).

20 mm × 29 mm × 32 mm in diameter. The postmenopausal bleeding became irregular and the amount of bleeding was reduced.

The patient was admitted to our hospital and transvaginal ultrasound revealed several small cyst locules detected inside the enlarged right ovary, with a maximum diameter of 7 mm. Laboratory examination revealed an elevated estradiol level of 64.90 pg/mL, a suppressed follicle-stimulating hormone (FSH) level of 5.25 IU/L and a luteinizing hormone (LH) level of 1.87 IU/L. The hormonal profile of the case also included normal testosterone, thyrotropin and progesterone in serum. Tumor markers, including CA125, CA199, alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA), were all within normal limits. A chest X-ray showed no evidence of pleural effusion or lung metastasis. An ovarian malignancy was not suspected, because of the atypical ovarian mass and negative tumor markers in serum. Some gynecologists suggested conservative observation, while others advocated oophorectomy. Informed consent was obtained from the patient. A diagnostic laparoscopy was initially performed, with the

finding of a 3 × 2 × 2 cm right ovarian mass and several small cysts inside the ovary. Hysteroscopy was also performed spontaneously, with the finding of a 0.5 × 0.6 cm endometrial polyp at five o'clock in the uterine cavity. Right oophorectomy, combined with endometrial polypectomy was performed. Frozen section investigation revealed a SLCT of the right ovary (Fig. 1A) and a laparotomy was performed with total hysterectomy, left oophorectomy, omentectomy, appendectomy, resection of infundibulopelvic ligament, peritoneal biopsies, and pelvic and para-aortic lymph nodes biopsies.

Pathological analysis confirmed a SLCT of the right ovary, with a high degree of differentiation (Fig. 1B). No areas of malignant transformation were identified on multiple sections of the surgical specimen. Immunohistochemical analysis showed a strong positive stain for inhibin-alpha, pan-cytokeratin (pan-CK) (Fig. 2A and B), and positive results for P53 (Fig. 3A). Five percent of tumor cells were positive for Ki-67 staining (Fig. 3B), whereas progesterone receptor (PR), estrogen receptor (ER), epithelial membrane antigen (EMA) and CD99 were negative (Fig. 3C–F).

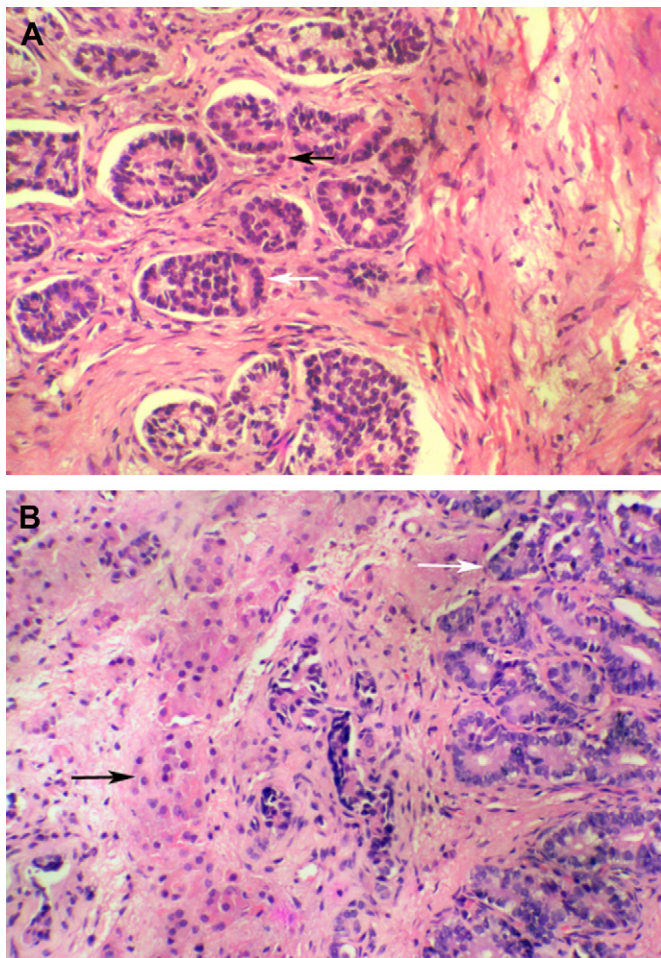


Fig. 1. Hematoxylin and eosin stains for the Sertoli–Leydig cell tumor (×200). (A) Photomicrograph of the frozen section; (B) photomicrograph of the paraffin section. Clusters of Leydig cells were large and polygonal with eosinophilic cytoplasm, as indicated by black arrows, which were next to the tubules of tumoral Sertoli cells, as indicated by white arrows.

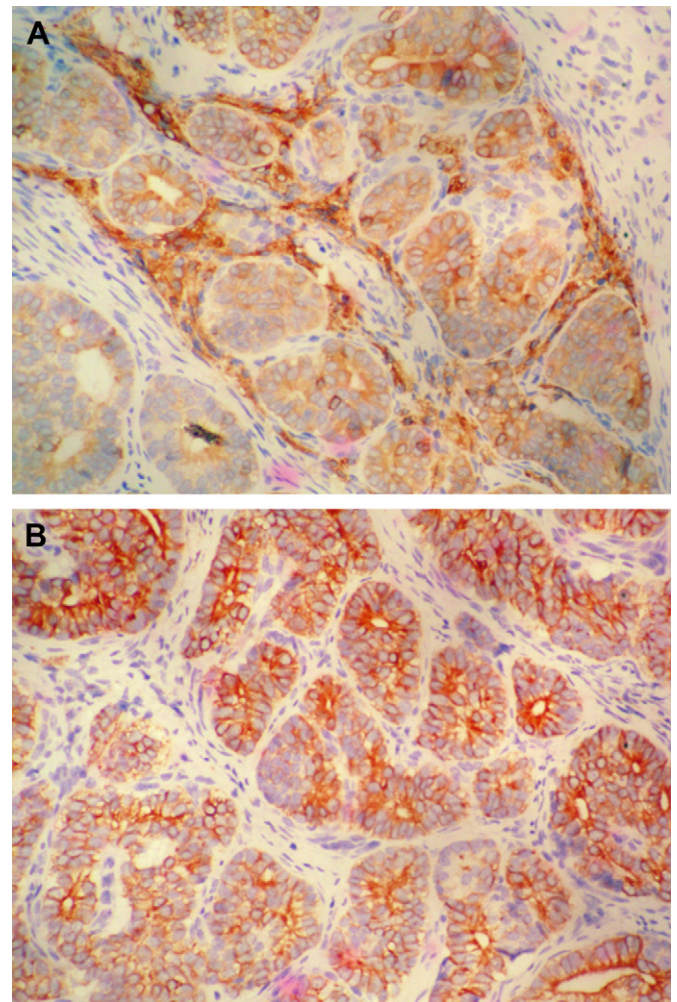


Fig. 2. Immunohistochemical analysis for the Sertoli–Leydig cell tumor (×400). (A) Strong inhibin-alpha immunoreactivity in Sertoli and Leydig cells; (B) strong positive stain of pan-cytokeratin in Sertoli cells.

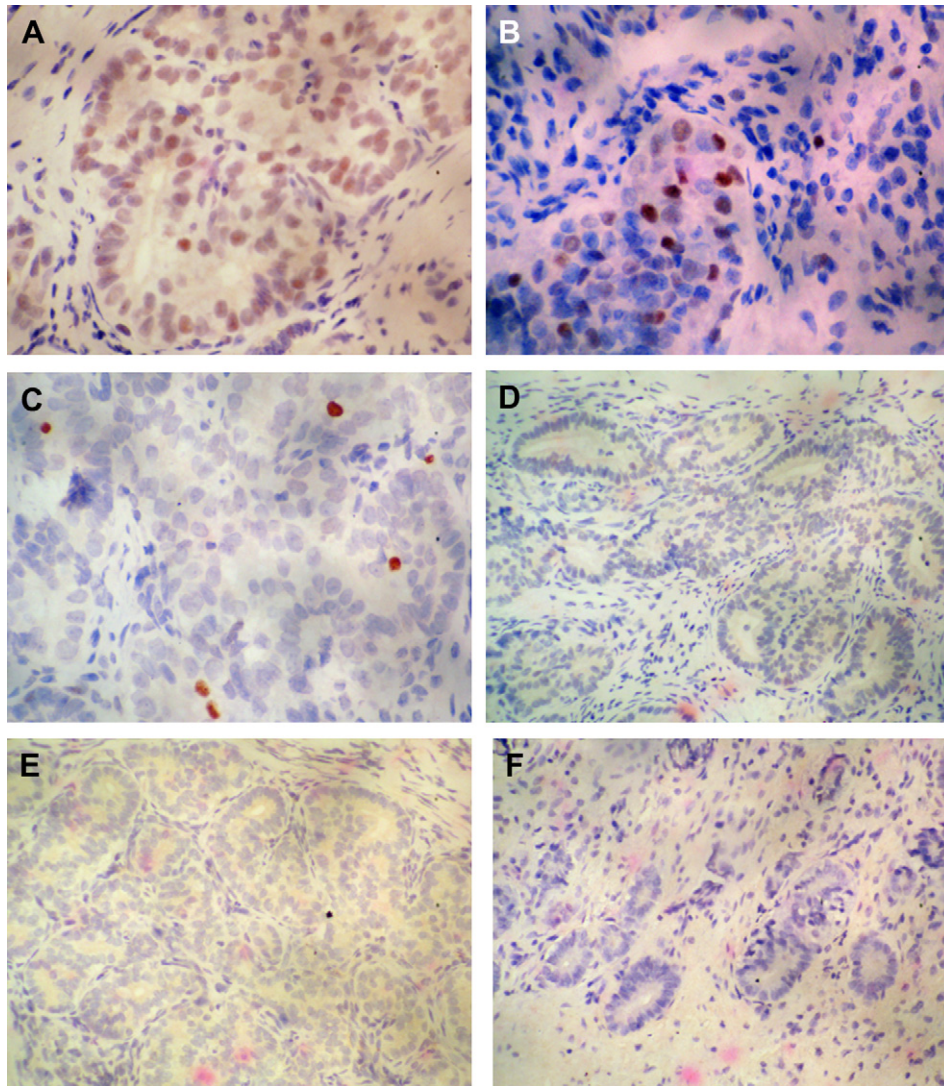


Fig. 3. Immunohistochemical analysis for the Sertoli–Leydig cell tumor ( $\times 400$ ). (A) positive stain of P53 in Sertoli cells; (B) positive in 5% of tumor cells with Ki-67 stain; (C) negative for stain of progesterone receptors; (D) negative for stain of estrogen receptors; (E) negative for stain of epithelial membrane antigen; (F) negative for stain of CD99.

The serum levels of estradiol, LH and FSH were normalized, and there was no sign of recurrence at her first follow-up visit 3 months postoperatively.

## Discussion

SLCT belongs to the group of SCST of the ovary, which is usually unilateral [1]. Young women with SLCT are usually characterized by virilization [6]. Occurrence in postmenopausal women is very rare [5]. Endocrine symptoms are absent from approximately half of patients and more than one-third of these patients develop signs of virilization, such as increasing facial hair growth, deepening of the voice, a dull pain in the lower part of the abdomen, and enlargement of the clitoris, by hormonal hyperproduction of testosterone, but they rarely present manifestations of hyperestrogenism.

In our case, the main clinical features were postmenopausal bleeding, endometrial hyperplasia and mucous polyp,

indicating hyperestrogenism in the patient. Hormone assays were dominated by high serum estradiol values and suppressed FSH and LH, which were consistent with the hyperestrogenic symptoms. The high production of estrogens in our patient with SLCT, was consistent with the observation of excessive secretion of estrogens in a nonhuman primate animal model, which might have originated in the hypertrophic thecal tissue rather than in the tumor [7].

We reviewed the literature on SLCT in postmenopausal women and found that there was only one out of 10 cases (10%) who presented with hyperestrogenism (Table 1). The patient, reported by Dhont et al in 1986, experienced postmenopausal bleeding, and endometrial mucous polyp and hyperplasia [5]. In another report, Young et al described that 5.6% patients (2/38) presented postmenopausal bleeding in patients with SLCT containing heterologous elements in the form of gastrointestinal-type epithelium [8], whereas Demidov et al reported that 20% (3/15) of SLCT patients had postmenopausal bleeding. However, a hormone profile was not

Table 1  
Review of the literature on Sertoli–Leydig cell tumor in postmenopausal women.

Authors	Year	Age (y)	Signs of hyperandrogenism	Signs of hyperestrogenism
Clinton et al [16]	1981	65	No	No
Dhont et al [5]	1986	73	No	Yes
Mango et al [17]	1988	59	Yes	No
Hansen and Sorensen [18]	1993	65	Yes	No
Cohen et al [19]	1993	60	Yes	No
Gheorghisan-Galateanu et al [9]	2003	69	Yes	No
Tampakoudis et al [20]	2004	71	No	No
Dahlgren et al [21]	2005	64	Yes	No
Caringella et al [22]	2006	65	Yes	No
Herrera et al [23]	2009	56	Yes	No

performed in these studies to confirm whether the symptoms were caused by elevated estradiol levels.

Immunohistochemistry is useful for the differential diagnosis of SLCT with other ovarian tumors [9]. In our case, tumor cells were positive for pan-CK, inhibin- $\alpha$ , and P53 protein, while Ki-67 was positive in 5% of tumor cells. Immunoassaying for PR, ER, EMA and CD 99 resulted in a negative reactivity in the tumor cells.

Increased production of inhibin was reported in SLCT [10], which was consistent with the immunohistochemical findings in our case. Furthermore, the association of positive staining for inhibin- $\alpha$  and negative staining for EMA supported the diagnosis of a SCST [11]. Negative results of ER and PR were reported to be a useful addition to traditional immunohistochemical markers, such as EMA, inhibin, CD99 and pan-CK, to distinguish Sertoli cell tumors from endometrioid tumors [12]. PR in our case was negative, although it was reported to be positive in 13% of Sertoli cell tumors [12]. In the present study, the expression of Ki-67 was positive in 5% of Leydig cells, while another study reported <2% [13]. The positive reaction for p53 antibodies observed in this study was consistent with findings in a 17- and a 33-year-old female in previous literature, which could probably be associated with the degree of gonadal development [14].

The tumor can be undetectable by pelvic ultrasound when it is small in dimensions, although ultrasound examination of the ovaries is recommended as the first choice of diagnostic procedure. SLCTs were either moderately or abundantly vascularized purely solid tumors or multilocular solid tumors with areas of innumerable closely packed small cyst locules mixed with solid areas [15]. The tumor in our patient was relatively small, but it presented several small cyst locules detected inside the right ovary, with a maximum diameter of 7 mm. The small dimension of the tumor was reported to be correlated with the good differentiation, while poorly differentiated tumors can reach up to 10–15 cm [4]. In this study, the high differentiation of SLCT could also be associated with its limited dimensions.

When SLCT patients had both a small ovarian mass and negative tumor markers in serum, as with the case in our study, it was possibly misdiagnosed with non-malignant disease. Conservative observation should be cautiously adapted, because it might delay the necessary surgical intervention. Furthermore, hyperestrogenism could be associated with

SLCT in a small portion of postmenopausal patients, although most patients have no endocrine symptoms or virilization.

In conclusion, the present study shows a postmenopausal case of SLCT, with well-differentiated pathology. The presenting manifestations of postmenopausal bleeding associated with hyperestrogenism in our case, might suggest the existence of a new specific type of endocrine complex disease.

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