Aegean Journal of Obstetrics and Gynecology

Case Report

Ovarian hilus cell hyperplasia and sertoli-leydig cell tumor in a patient with postmenopausal virilization: a rare case report

Begüm Ertan [a, †], Eyuphan Ozgozen[a], Orkun Ilgen [a], Goksenil Bulbul [b], Bahadır Saatlı [a], Cagnur Ulukus [b]

[a] Department of Obstetrics and Gynecology, Dokuz Eylul University School of Medicine, Izmir, TURKEY

[b] Department of Pathology, Dokuz Eylul University School of Medicine, Izmir, TURKEY

ABSTRACT

Objective: We present a case report regarding a 71-year-old woman with postmenopausal virilization caused by ovarian hilus cell hyperplasia and Sertoli-Leydig cell tumor(SLCT) who was suffered from hair loss, clitoromegaly and hirsutism.
Case Report: The patient's plasma total testosterone level was 351.24ng/dL . In the magnetic resonance imaging examination, a nodular formation of 20x26mm in size was observed in the right ovary. At the transvaginal ultrasound, a cystic mass of 28x28mm was seen in the right ovary. Then we performed a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy. The final pathology showed a poorly differentiated SLCT at the right ovary and hilus cell hyperplasia at the left ovary. SLCTs, which are relatively less common, are extremely rare to be seen in the postmenopausal period.
Conclusion: What distinguishes this case from others is that SLCT and hilus cell hyperplasia may cause virilization symptoms together, in addition to its prevalence in advanced age.
Keywords: sertoli-leydig cell tumor; ovarian hilus cell hyperplasia; postmenopausal virilization; sex-cord-stromal tumors

ARTICLE INFO
Doi: 10.46328/aejog.v3i3.99

Article history:
Received: 29 August 2021
Revision received: 5 October 2021
Accepted: 9 November 2021

Introduction

Virilization is a rare condition in postmenopausal hirsutism and is associated with a high androgen level measured in the blood. When such a clinic emerges, the first thing that should come to mind is to rule out adrenal or ovarian malignancies. Although rare, hilus cell tumors should also be considered [1]. Hilus cell hyperplasia is a less common cause of this condition [2]. Sertoli-Leydig cell tumors (SLCT), also knows as androblastoma, belong to the category of sex cord-stromal tumors. SLCT of the ovary is a significantly rare neoplasm accounting for <0.5% of all primary ovarian neoplasms [3]. Although it is seen in any age group between 2 and 75 years old, it is frequently seen in the 2nd - 3rd decade. As it can be clinically asymptomatic, it may show clinical differences in measurements ranging from severe virilizing findings. Androgenic activity is observed in about half of the cases. The tumor is often seen unilaterally and is diagnosed in 80% of cases when they are at stage 1. The prognosis of SLCT is generally promising, but it is closely related to the stage and grade of the tumor. It is clinically malignant in approximately 10% of cases. Pathologically, the presence of heterologous elements is associated with a poor prognosis. Recurrence is usually within 2 years and occurs in the peritoneal cavity [4].

The definition of anaplasia in cases with histologically moderate change is associated with a poor prognosis and no other poor prognosis criteria have been defined [5].
We present a rare case report of advanced age, postmenopausal patient with hirsutism detected clinically and a mass in the ovary determined by imaging methods, but later detected SLCT in the right ovary and hilus cell hyperplasia in the left ovary.

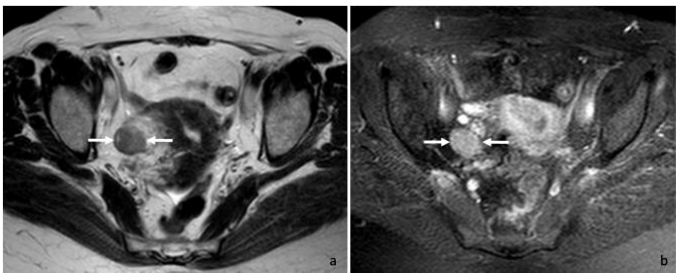
Case Report

A 71-year-old female suffered from hair loss, clitoromegaly and hirsutism started 5-6 months ago. The gravidity and parity of the patient are G8P3. The patient has been in menopause for 25 years and the first menstruation was at the age of 14. The patient's menstruation was regular in the reproductive period and there was no complaint of any hirsutism and virilization. In the postmenopausal period, there was no complaint other than mild-moderate hot flashes until the virilization findings started 5-6 months ago. Other diseases of the patient were hypothyroidism and adrenal adenoma. The patient was performed from thyroid gland, laparotomic cholecystectomy, and dilatation&curettage for 5 times. Due to these new and sudden onset complaints, the patient was first referred to the endocrinology outpatient clinic. During the physical examination, hirsutism findings have occurred especially under the chin, upper back, and around the chest. Ferriman- Gallwey's score was 14 out of 36. Cliteromegaly was detected in the pelvic examination.

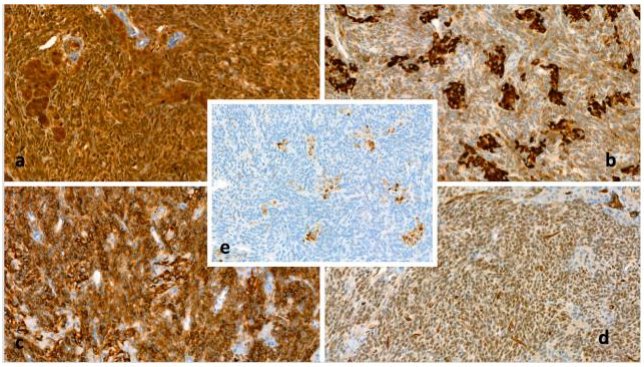
† Corresponding author.
E-mail: begmertan@hotmail.com
OrcID: 0000-0002-0370-7509

Laboratory tests showed that the initial value of cortisol was 25.34 ug/dL, SHBG(sex hormone binding globulin) was 57.80 nmol/L, 1,4-Delta Androstenedione was 3.91 ng/mL, ACTH(adrenocorticotropic hormone) was 18.10 pg/mL, total testosterone was 351. 24 ng/dL, FSH(follicle-stimulating hormone) was 35.44 mIU/mL, LH(luteinizing hormone) was 29.15 mIU/mL, estradiol was 54.30 pg/mL. Dexamethasone suppression test was negative.
The endocrinologist noted that it is not compatible with the clinical findings of the patient with Cushing syndrome, Conn syndrome, or pheochromocytoma. The fecal occult blood test was negative, either. Tumor markers(AFP(alpha fetoprotein), CEA(carcinoembryonic antigen), CA(cancer antigen) 125, CA-19-9 and CA15-3) were negative. At the MRI(magnetic resonance imaging) scan, the uterus has an anteverted appearance. An appearance compatible with uterine leiomyoma with a size of approximately 2 cm was observed in the left anterior inferior in the uterus. A nodular formation of 20x26mm in size was observed in the right ovary (Figure 1). The left ovary was atrophic. At the transvaginal ultrasound, the uterus is in large appearance. In the uterine fundal section, an appearance compatible with the 2 cm myoma uteri was observed. Endometrium was observed in normal thickness. A cystic mass of 28x28mm was seen in the right ovary. The left ovary was atrophic. We performed an endometrial biopsy. The pathology resulted in an atrophic endometrium. Then we performed a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy. The frozen section found out SLCT at the right ovary. The final pathology showed a poorly differentiated SLCT at the right ovary and hilus cell hyperplasia at the left ovary. The tumor was at stage IA of the 2014 classification of the International Federation of Gynecology and Obstetrics (FIGO).

Figure 1: T2-weighted image (a) of the patient demonstrating a low signal intensity mass (arrows) in the right ovary which shows contrast enhancement on post-contrast fat saturated T1-weighted image (b)

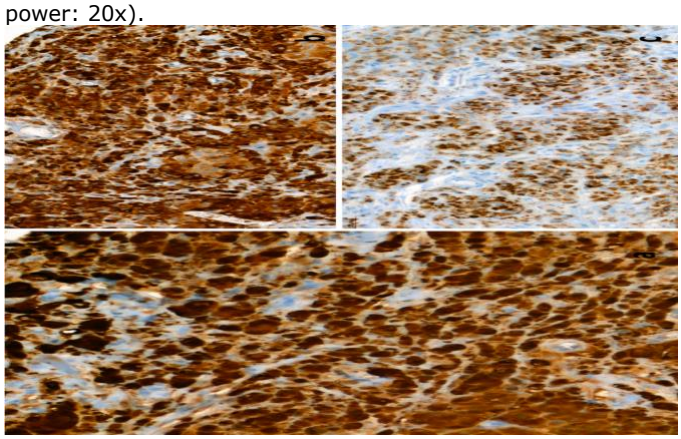


Surgical Specimen and Histopathology
Light microscopic examination of the right ovary revealed a tumor was generally composed extensively of solid sheets of poorly differentiated Sertoli cells -which may resemble a fibrosarcoma, an undifferentiated carcinoma, or a primitive germ cell tumor- with scattered clusters of Leydig cells. Sertoli cells were in medium size, showed pleomorphism, had scant cytoplasm, irregular nuclear membrane, and inconspicuous or mild prominent nucleoli.
Immunohistochemically, in the right ovary, neoplastic cells stained positive for calretinin, inhibin, CD56, WT-1, and Melan-A (Figure 2); negative for MOC31, Pancytokeratin, and EMA.
Figure 2: Immunohistochemical examination of right ovary, poorly differentiated Sertoli Leydig Cell Tumor. (a) The neoplastic cells are positive for calretinin (magnification power: 20x). (b) The neoplastic cells are positive for inhibin (magnification power: 20x). (c) The neoplastic cells are positive for CD56 (magnification power: 20x). (d) The neoplastic cells are positive for WT-1 (magnification power: 20x). (e) The neoplastic cells are focal positive for Melan-A (magnification power: 20x).



In the left ovary, hilus cells also stained positive for calretinin, inhibin, and Melan-A (Figure 3); negative for EMA. Based on the histopathological and immunohistochemical findings; a poorly differentiated SLCT in the right ovary and hilus cell hyperplasia diagnoses in the left ovary were established.

Figure 3: Immunohistochemical examination of left ovary, Hilus cell hyperplasia. (a) The hilus cells are immunoreactive for calretinin (magnification power: 20x). (b) The hilus cells are immunoreactive for inhibin (magnification power: 20x). (c) The hilus cells are immunoreactive for Melan-A (magnification power: 20x).



Discussion

SLCT is a rare ovarian cancer and it is seen more frequently between the ages of 20-30 on average [5]. Macroscopically, the size ranges from 2 to 35 cm and may be solid, solid-cystic, or rarely cystic. It is mostly frequently encountered as well and moderately differentiated tumors histologically [6]. In tumors with moderate differentiation, endodermal elements are more frequently observed, and mesenchymal structures are more frequently observed in association with poorly differentiated tumors. The prognosis of SLCT is generally promising, but stage and level of differentiation are significantly associated with prognosis and recurrence [7]. The clinically malignant tumors were detected in %19 of the tumors with heterologous elements in a study by Young and Scully [7]. Adjuvant chemotherapy is recommended for patients with advanced-stage, intermediate and poor differentiation, retiform pattern, and presence of heterologous elements [8]. Many studies show that SLCTs can be seen in every decade of life, especially in the second and third decades [4,8]. However, the age of clinical presentation in our case was 71. According to Durmuş et al. conducted with 17 patients, 5 patients (29.4%) had an androgenic clinic. (oligomenorrhea, amenorrhea, hirsutism, clitoromegaly) 6 patients (35.3%) had estrogenic manifesto (postmenopausal bleeding, menometrorrhagia) and 6 patients (35.3%) non-hormonal manifestation (abdominal pain, abdominal distension). In our case, our patient had an androgenic clinic and had no post-menopausal bleeding or other non-hormonal findings [9].

Rutgers and Scully et al. have described hilus cell hyperplasia in bands adjacent to ovarian cysts or tumors. More than half of these identified patients were accompanied by virilization symptoms [7]. Also, the relationship between hilus cell hyperplasia and virilization is not clear. In affected patients, oophorectomy improves androgen excess, alternative therapies have been reported and oophorectomy is not the only treatment method. AFP is a glycoprotein detected at low levels in the blood of healthy adult patients. It is the main source of the yolk sac and liver production during the fetal period. AFP levels above normal in adulthood may be evidence of hepatocarcinoma and germ cell tumors. Moreover, it may suggest an ovarian or testicular tumor. This glycoprotein has already been studied extensively as a tumor marker and is routinely used both in diagnosis and in follow-up.

Schneider et al. found ovarian SLCT with a high level of AFP secretion in some patients [10].

According to the study of Sigismondi et al., AFP values were measured in 13 patients SLCT group, and AFP values were found high in 3 patients [11]. According to the study conducted by Castro et al., which included 12 SLCT patients, increased levels of AFP were measured in 5 patients. Moreover, a more advanced stage and a more difficult treatment were encountered in these patients at the time of diagnosis. In our case report, CEA, CA125, CA 19-9, CA 15-3 were normal, including AFP. SLCT treatment is still a controversial subject because our knowledge about this disease is limited and the factors affecting the prognosis of the patient are not known exactly. According to Colombo et al., surgery is the standard and primary approach for this disease [12]. Because many SLCT cases are unilateral and limited to the ovary. Unilateral salpingo-oophorectomy and staging is an adequate treatment for these patients in cases where there is no extra ovarian disease and who want the preservation of fertility. Many authors emphasize that endometrial evaluation is particularly important in these patients due to concomitant endometrial neoplasia. According to the study by Colombo et al., in cases of more advanced disease or bilateral tumors, hysterectomy and bilateral salpingo-oophorectomy and meticulous surgical staging are required in postmenopausal women [12]. Moreover, the examination of the abdominal cavity, cytological sampling from intraabdominal free fluid, peritoneal biopsy, omentectomy, and pelvic-paraaortic lymph node dissection are recommended. However, the place of surgical staging is controversial, and the benefits of a detailed surgical staging should be considered in addition to the severe morbidity it creates. Brown et al. emphasized that lymphadenectomy may be neglected in order not to increase the potential surgical risk, since lymph node metastasis appears very rarely in sex-cord stromal tumor patients [13]. In our patient, we performed a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy with frozen pathology. The frozen pathology result was found as a SLCT at the right ovary and the left ovary showed no malignancy. The abdominal cavity was examined and no abnormality was found. Peritoneal biopsy and lymph node sampling were not performed to avoid additional surgical morbidity to the patient. No complications were encountered during the inpatient follow-up. Blood test after 5 days after the surgery was cortisol 12.08 ug/dL, total testosterone <7.00 ng/mL, DHEA-SO4(dehydroepiandrosterone-sulfate) 28.05 ug/dL. The patient remains under surveillance.

In the study performed by Colombo et al., it was stated that adjuvant chemotherapy should be given in poorly differentiated SLCTs, heterologous elements containing SLCTs, and advanced-stage patients [12]. In the study conducted by Castro et al., adjuvant therapy was applied to 2 out of 12 patients and the tumors were poorly and moderately differentiated. Recurrence was not observed in any patient [14]. In the study conducted by Schneider et al., only 1 patient received adjuvant therapy in 24 stage 1A patients (including moderate and poor differentiation), and no recurrence was observed in any patient [10]. However, to understand the correct indication of adjuvant therapy, we need to understand the prognostic factors that affect this disease. And, randomized controlled trials should be designed in these SLCT patients. The main reason for this limitation is that this disease is very rare, occurs in a wide age range, and appears in different stages. In our case, adjuvant therapy was not considered for the patient. It was planned to follow the patient clinically and radiologically.

SLCT is generally a disease with a good prognosis. Moreover, since adjuvant therapy may come the next day, examining heterologous elements and searching for the presence of anaplasia is of critical importance for these patients.

Also, the follow-up of these patients is very important to detect and intervene in the early stage of recurrence.

With this case report, we see that SLCT is a condition that can be encountered in elderly patients.

We believe that case reports of such rare cases will help us take our current knowledge to the next level. Thanks to more reporting of such rare diseases, they will have a positive contribution to the completion of our missing information.

Statement of ethics: This report followed guidelines to be HIPAA compliant and permission was obtained from the patient to publish identifiable photographs. The study adhered to the tenets of the Declaration of Helsinki.

Acknowledgments: We would like to thank Dr. Tevfik Demir(University of Dokuz Eylul) and Dr. Mustafa Secil (University of Dokuz Eylul) for comments on the manuscript. The authors declare that they have no conflicts of interest.

Disclosure

Authors have no potential conflicts of interest to disclose.

References

[1] Surrey ES, de Ziegler D, Gambone JC, Judd HL. Preoperative localization of androgen-secreting tumors: clinical, endocrinologic, and radiologic evaluation of ten patients. American journal of obstetrics and gynecology. 1988 Jun;158(6 Pt 1):1313–22.

[2] Braithwaite SS, Bitterman P, DeGeest K, Lebbin DR. Postmenopausal virilization, simple ovarian cyst, and hilus cell hyperplasia--is there an association? Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2001;7(1):40–3.

[3] Prat J. Pathology of cancers of the female genital tract. International Journal of Gynecology & Obstetrics. 2012;119:S137–50.

[4] Bhat RA, Lim YK, Chia YN, Yam KL. Sertoli-Leydig cell tumor of the ovary: analysis of a single institution database. The journal of obstetrics and gynaecology research. 2013 Jan;39(1):305–10.

[5] Kurman RJ, Cancangiu ML, Herrington CS YR. No Title. 4th Ed. Lyon: International Agency for Research on Cancer; 2014.

[6] Nouriani M, Felix J, Dubeau L. Histogenesis and histopathological characteristics of Sertoli-Leydig cell tumors. CME Journal of Gynecologic Oncology. 2002 Jul;7:114–20.

[7] Young RH, Scully RE. Ovarian Sertoli-Leydig cell tumors. A clinicopathological analysis of 207 cases. The American journal of surgical pathology. 1985 Aug;9(8):543–69.

[8] Gui T, Cao D, Shen K, Yang J, Zhang Y, Yu Q, et al. A clinicopathological analysis of 40 cases of ovarian Sertoli-Leydig cell tumors. Gynecologic oncology. 2012 Nov;127(2):384–9.

[9] Durmuş Y, Kılıç Ç, Çakır C, Yüksel D, Boran N, Karalök A, et al. Sertoli-Leydig cell tumor of the ovary: Analysis of a single

institution database and review of the literature. The journal of obstetrics and gynaecology research. 2019 Jul;45(7):1311–8.
[10] Schneider DT, Orbach D, Cecchetto G, Stachowicz-Stencel T, Brummel B, Brecht IB, et al. Ovarian Sertoli Leydig cell tumours in children and adolescents: an analysis of the European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT). European journal of cancer (Oxford, England : 1990). 2015 Mar;51(4):543–50.
[11] Sigismondi C, Gadducci A, Lorusso D, Candiani M, Breda E, Raspagliesi F, et al. Ovarian Sertoli-Leydig cell tumors. a retrospective MITO study. Gynecologic oncology. 2012 Jun;125(3):673–6.
[12] Colombo N, Parma G, Zanagnolo V, Insinga A. Management of ovarian stromal cell tumors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007 Jul;25(20):2944–51.
[13] Brown J, Sood AK, Deavers MT, Milojevic L, Gershenson DM. Patterns of metastasis in sex cord-stromal tumors of the ovary: can routine staging lymphadenectomy be omitted? Gynecologic oncology. 2009 Apr;113(1):86–90.
[14] Castro BGR, Souza C de P, Andrade CEM da C, Vieira M de A, Andrade DAP de, Reis R dos. Ovarian Sertoli-Leydig Cell Tumors: Epidemiological,Clinical and Prognostic Factors. Revista Brasileira de Ginecologia e ObstetrÃ\-cia. 2019;41:440-8