Gynecologic Oncology Reports 52 (2024) 101345

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Leydig tumor in normal sized ovaries causing clitoromegaly: A case report

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ARTICLE INFO

Keywords:
Leydig stromal cell tumor
Hyperandrogenism
Clitoromegaly
Case report

ABSTRACT

We describe an unusual presentation of a rare Leydig tumor presenting in bilateral ovaries that are otherwise normal in size for postmenopausal women. A 66-year-old woman presented with postmenopausal bleeding and during her work-up acutely developed clitoromegaly. Her diagnostic work-up revealed a 1.8 cm left ovarian complex cyst and extremely elevated testosterone levels. Management included hysterectomy and bilateral salpingo-oophorectomy. Final pathology revealed Leydig tumors in the bilateral ovaries. This case discusses a rare presentation of a rare tumor and highlights the importance of a thorough examination of the female genitalia and investigation for root cause.

1. Introduction

While traditionally thought of as testicular neoplasms, Leydig tumors can arise in the ovaries. They are in the class of steroid cell tumors, which themselves are a type of sex cord stromal tumor. Sex cord stromal tumors represent approximately 7 % of all primary ovarian tumors, and steroid cell tumors are estimated to make up less than 0.1 % of those. (Horta and Cunha, 2015; Prat et al., 2014) Leydig cell tumors themselves are diagnosed in 15 % of cases of steroid cell ovarian neoplasms, making their existence unknown to many general gynecologists.(Prat et al., 2014) They are typically unilateral and unlike Sertoli-Leydig cell tumors, Leydig cell tumors exclusively secrete testosterone. Therefore, the increase in other steroids like androstenedione and dehydroepiandrosterone is not typically seen on laboratory analysis.(Prat et al., 2014; Nagamani et al., 1989) Classic clinical features of these tumors include virilization and hirsutism in up to 80 % of cases and the mean age of presentation is 58.(Prat et al., 2014) They are typically diagnosed during workup for signs of androgen excess or incidentally found as a pelvic mass on imaging.(Kozan et al., 2014; Klimek et al., 2020; Aminimoghaddam et al., 2012; Patidar et al., 2019) Treatment is surgical, with bilateral salpingo-oophorectomy being the standard procedure for postmenopausal patients.(Suturina et al., 2022).

2. Case report

A 66-year-old gravida 1 para 1 woman presented to the gynecology clinic for intermittent postmenopausal spotting over the prior year. The patient's only other complaint was anal pressure but without constipation or blood in the stool. She had no personal or family history of malignancies. Her initial in-clinic physical exam revealed an overweight woman with normal external female genitalia without signs of androgen excess. The uterus was about 10-week size, and there were no palpable adnexal masses although there was focal tenderness in her right levator ani muscle. On transvaginal ultrasound, the uterus was 10.8 x 6.9 x 6.2 cm with 2 small fibroids, as well as a well circumscribed heterogenous lesion which measured 4.6 x 2.3 x 4.3 cm filling the endometrial cavity (Fig. 1a). The left ovary was not visualized and the right ovary was measured to be 1.7 x 1.2 x 1.7 cm (Fig. 1b). In-office endometrial biopsy revealed a benign endometrial polyp on final pathology. She was counseled on and agreed to a hysteroscopy with polypectomy.

Two weeks later at her scheduled hysteroscopy, significant clitoromegaly to 6 x 2 cm was noted. Her hysteroscopy did not reveal any intracavitary lesion as described in the ultrasound likely because of the flat nature of the lesion arising from the endometrial wall without protrusion into the endometrial cavity, though a curettage specimen obtained at the time found fragments of a benign polyp. Two more weeks later at the postoperative visit, she noted that she felt more discomfort due to clitoromegaly with rubbing of underwear. Work up revealed elevated testosterone level of 945.2 ng/dL (normal range: 10.0–75.0 ng/dL) and a normal androstenedione (DHEA-S) level of 61 mcg/dL (normal range: 9–118 ng/dL). She also had erythrocytosis with a peak hemoglobin level of 16.5 gm/dL (normal range 11.3–15.0 gm/

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https://doi.org/10.1016/j.gore.2024.101345
Received 3 January 2024; Received in revised form 14 February 2024; Accepted 17 February 2024
Available online 21 February 2024

dL) hematocrit level of 47.6 % (normal range: 33.6–44.6 %). A computed tomography scan was also obtained to rule out adrenal source of androgen excess in the setting of normal appearing ovaries and was unremarkable. A repeat transvaginal ultrasound was obtained as previous one did not visualize the left ovary. This second sonogram again reimaged the intracavitary lesion, roughly the same size as measured prior, and was able to visualize the left ovary which measured 3.8 x 1.6 x 2.2 cm with a hypoechoic cystic lesion of 1.8 x 1.7 x 1.4 cm (Fig. 1c). The right ovary measured 2.2 x 1.2 x 1.5 cm on that second scan. The patient was counseled on bilateral salpingo-oophorectomy as well as a concurrent hysterectomy to evaluate for testosterone secreting tumor and to assess the persistent endometrial mass. Patient agreed to proceed with total robotic hysterectomy with bilateral salpingo-oophorectomy. The surgical findings included grossly benign appearing uterus and ovaries, with 4 cm submucosal fibroid that matched the findings of the ultrasound. The frozen section of the ovary revealed 2 small nodules with bland eosinophilic cells, favoring sex cord-stromal tumor but could not assuredly determine the origin. Lymph node sampling was performed for this reason. The remainder of the operation and postoperative course were uncomplicated.

The lesions were completely resected without any evidence of local spread. Sampled lymph nodes were also negative for disease. Histopathologic examination showed two tan-brown nodules with a solid cut surface, 2.0 cm (Fig. 2a) and 0.6 cm (Fig. 2b), in the left and right ovaries respectively. The sections showed well-circumscribed nodules (Fig. 3a) composed of cells with abundant eosinophilic cytoplasm, round nuclei

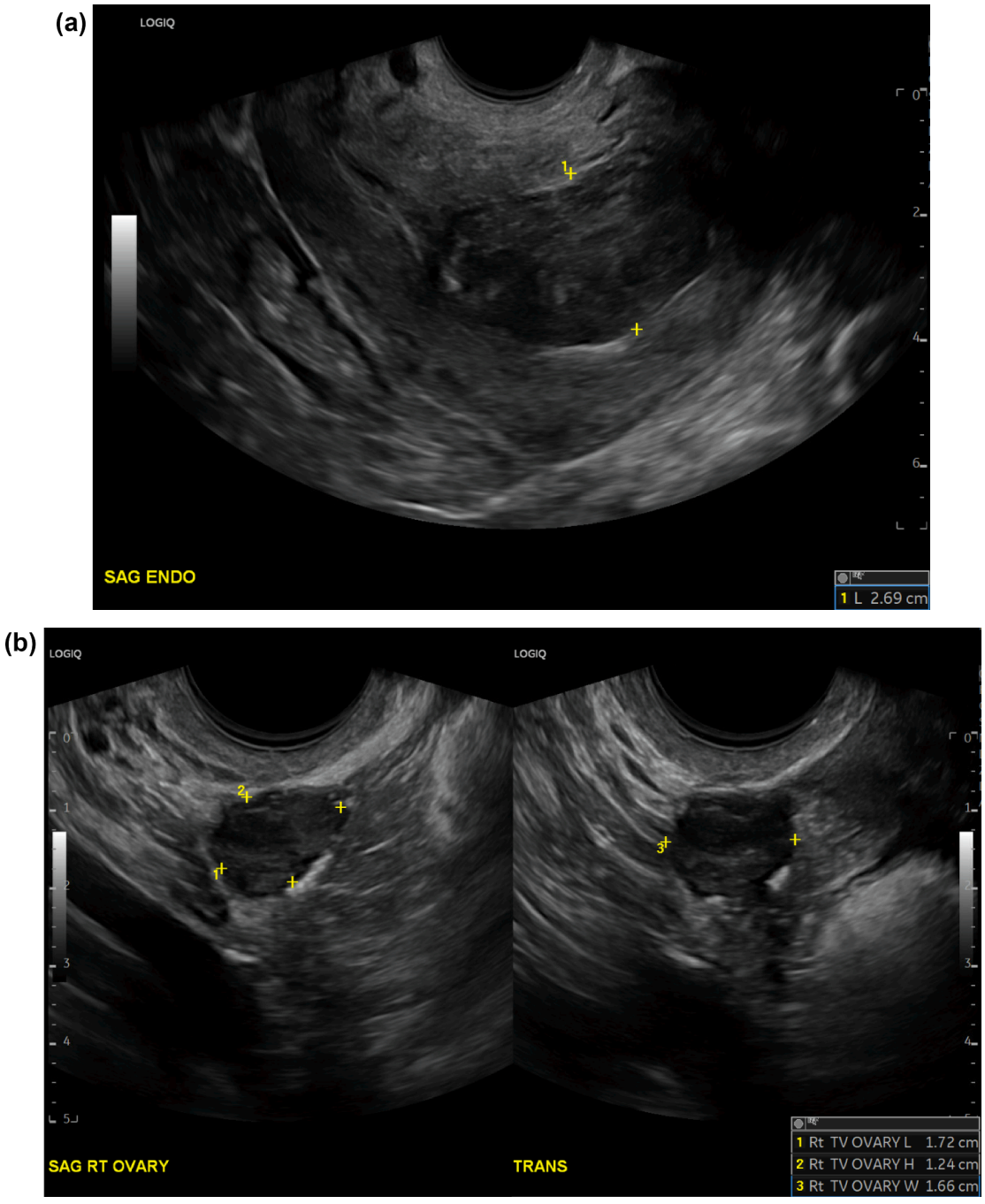

Fig. 1. (a) Sagittal ultrasound demonstrating intracavitary mass. (b) Two views of right ovary normal in size. (c) Two views of left ovary and associated hypoechoic lesion.

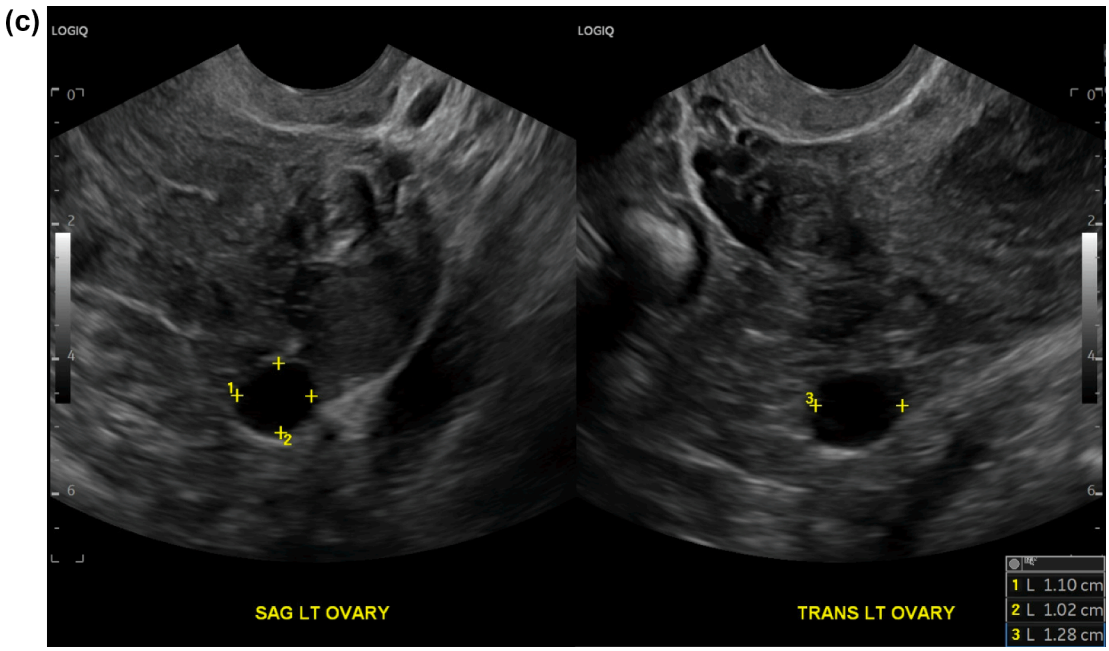

Fig. 1. (*continued*).

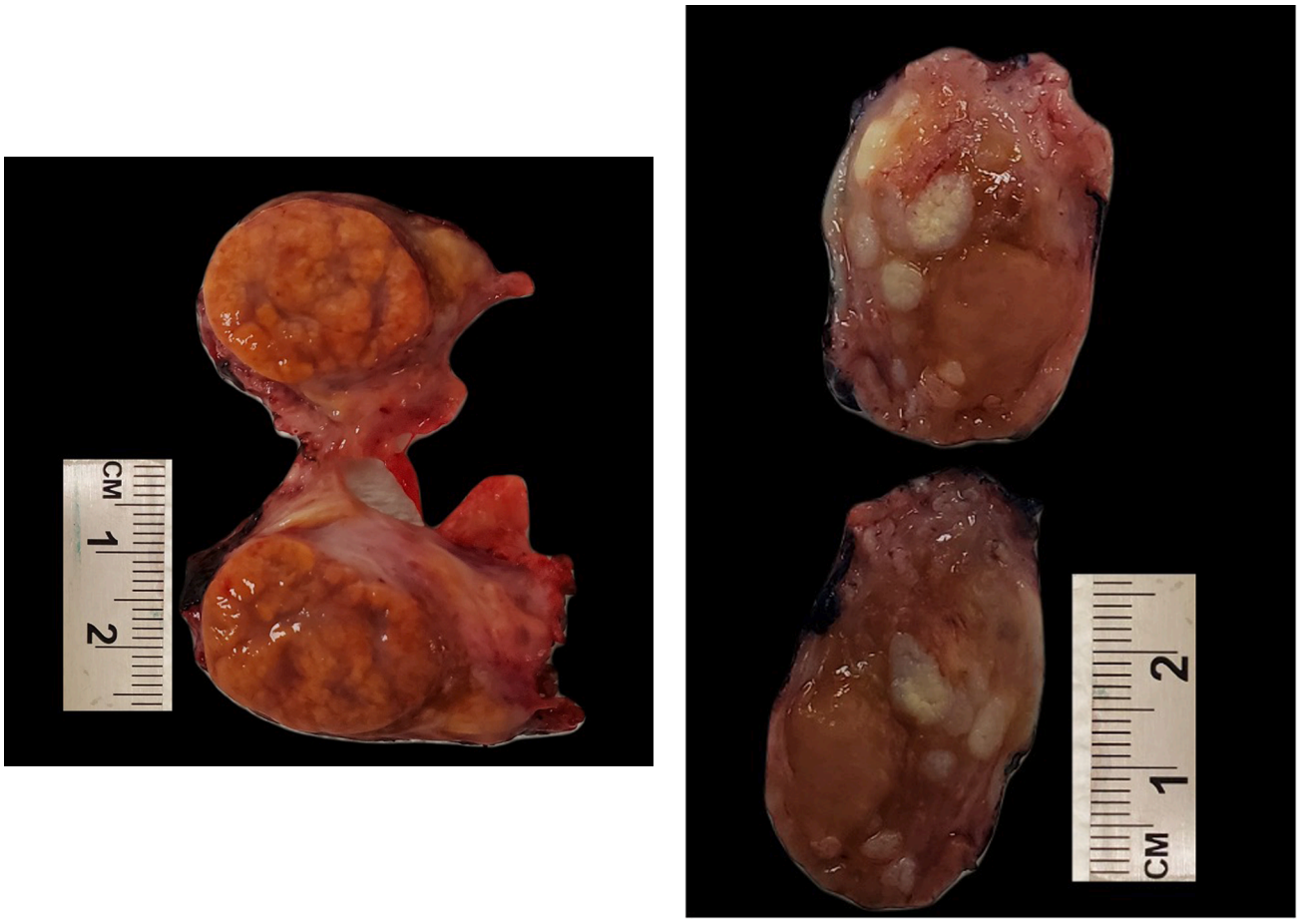

Fig. 2. (a) Gross specimen bisected showing tan-brown nodule in left ovary. (b) Gross specimen bisection showing tan-brown nodule in right ovary.

with a single prominent nucleolus (Fig. 3b). Mitoses were very rare. Scattered Reinke crystals (Fig. 3c) were noted. The tumor cells were positive for calretinin (Fig. 4), consistent with a Leydig cell tumor. The uterine specimen contained leiomyomatous disease but was otherwise unremarkable.

Follow-up exams demonstrated serial decrease in clitoromegaly,

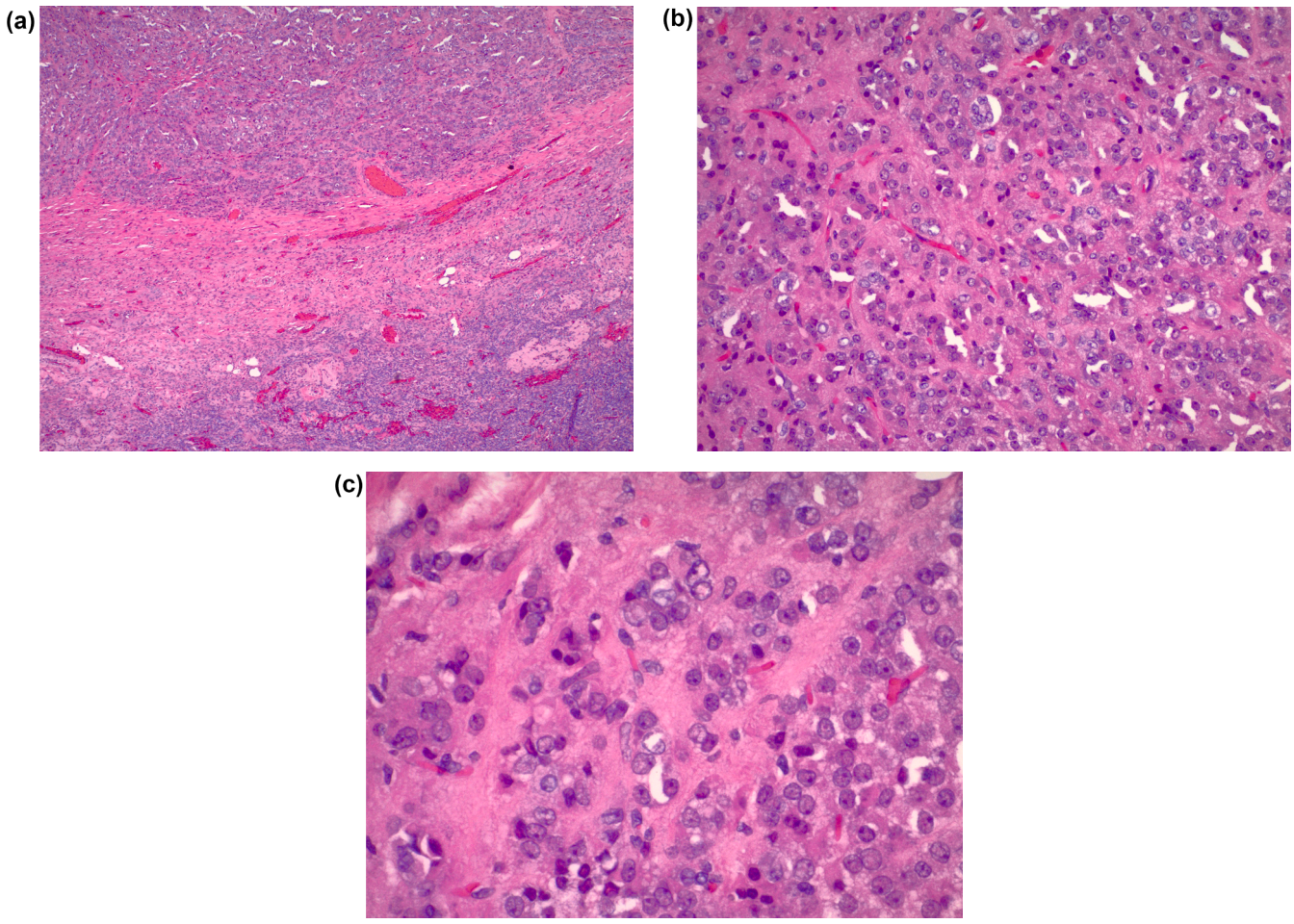

Fig. 3. (a) Hematoxylin and eosin staining of ovarian lesion demonstrating well-circumscribed nodules. (b) Cells with abundant cytoplasm and round nuclei with single prominent nucleolus. (c) Numerous scattered Reinke crystals within tumor cell cytoplasm.

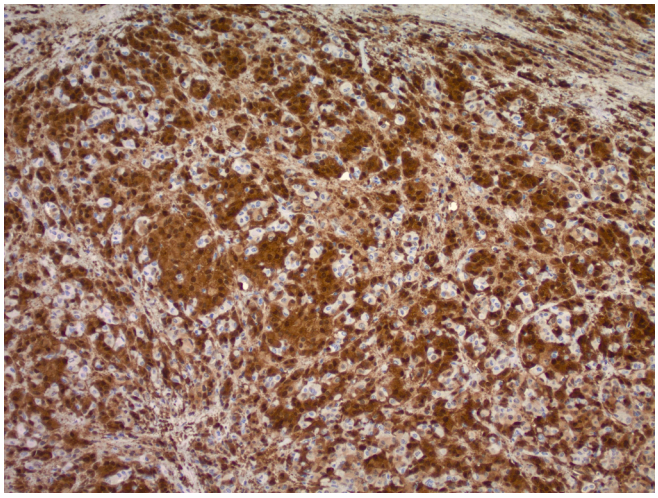

Fig. 4. Profuse immunohistochemical staning for calretinin within the tumor cells.

though specific measurements were not documented in the chart. The patient's testosterone levels at one week and at seven months post-operatively were both undetectable.

3. Discussion

Androgen excess is uncommon in postmenopausal women though the natural course of menopause is to have a rapid decline in estrogen production with a gradual decline in androgen secretion. Therefore, signs of hyperandrogenism should prompt evaluation. Common pathologies in this age group include congenital adrenal hyperplasia, obesity-induced hyperandrogenism, ovarian hyperthecosis, medication effect, or tumors arising from the adrenal glands or ovaries.(Zaman and Rothman, 2021) Ovarian Leydig cell tumors are a rare, benign cause of hyperandrogenism. They account for less than 0.1 % of all ovarian neoplasms and are predominantly unilateral and found in the ovarian hilum.(Horta and Cunha, 2015; Prat et al., 2014) They are often found as small, hyperechogenic masses on ultrasonographic imaging, measuring up to 3 cm.(Demidov et al., 2008) Leydig cell tumors are predominantly benign lesions, though as many as 20 % of cases have local, peritoneal metastasis with distant metastasis being rare.(Bala et al., 2022).

Here we describe a case of bilateral Leydig cell tumors, both within ovaries within the normal range of volume for a postmenopausal female being evaluated for postmenopausal bleeding. Despite repeated ultrasounds demonstrating an intracavitary lesion, sonographic appearance of the ovaries was nonspecific and hysteroscopic evaluation was unremarkable. The discrepancy between the sonographic reports and the hysteroscopic procedural findings could be attributed to the limited resolution of ultrasound as well as the location of the lesion.

These tumors with abundant eosinophilic cytoplasm are categorized as steroid cell tumors and "lipid cell tumor" is often used as a morphologic description. The differential diagnoses in this category is usually

based on size, location and the clinical presentation. Stromal luteomas usually present with estrogenic symptoms and rarely with androgenic symptoms. Morphologically they are composed of neoplastic cells with pink to vacuolated-pale cytoplasm; surrounding this centrally placed neoplasm is preserved ovarian cortex. Luteinized granulosa-theca cell tumors and luteinized thecomas may be considered in the differentials but these are recognized by the presence of the non-luteinized component of the tumor. Leydig cell tumors occur in the hilus and are rare in the stroma. These are defined by the presence of crystalloids of Reinke. Approximately two thirds of steroid cell tumors cannot be classified specifically as stromal luteomas or Leydig cell tumors and these are then classified as Steroid cell tumors not otherwise specified (NOS). Stromal luteomas and Leydig cell tumors have a benign course, in contrast, the steroid cell tumors NOS have a varied course, some have been reported to extend beyond the ovary at the time of diagnosis with others demonstrating a malignant course.(Hayes and Scully, 1987) In our patient, lymph node biopsies were obtained due to the uncertainty of exact histology on frozen section, though sex cord-stromal tumors rarely metastasize to the lymphatic system.(Kleppe et al., 2014) If there is more certainty that the pathology is a pure Leydig cell tumor, then lymph node assessment is not needed nor recommended.(Brown et al., Apr).

Bilateral Leydig tumors have been described eleven prior times in the literature with our patient being the twelfth report.(Sanz et al., 2006; Shakir et al., 2021; Hussain et al., 2021; Langevin et al., 2020) The most intriguing feature of our case is the marked and rapid development of clitoromegaly that triggered the work up leading to the diagnosis. Rarely do clinicians have the opportunity to witness first-hand the genesis of a disease, and even less so in one as rare as this. To our knowledge, prior reports of Leydig cell tumors have not described the time course in the development of physical features of the disease as the patients in those reports had been referred to specialists after their symptoms had been present for a while. Additional laboratory studies discovered erythrocytosis in our patient, which has been described in association with testosterone excess and its effect on increasing erythropoietin and suppressing hepcidin.(Kozan et al., 2014; Bachman et al., 2014) However, our patient did not exhibit any other symptoms associated with hyperandrogenism such as male-type alopecia, hirsutism, or voice changes, likely due to the early nature of her disease.

Our case highlights the importance of thorough pelvic examination leading to the work up for androgen excess as well as consideration of steroid cell tumors causing androgen excess even if ovaries appear grossly normal size. Our patient was being evaluated and treated for postmenopausal bleeding and found to have androgen excess, which is not normally a presenting complaint for Leydig cell tumors which exclusively secrete androgens which do not affect the endometrial lining.(Zaman and Rothman, 2021) As has been often noted in prior reports on this disease, radiographic studies alone are not enough to diagnose ovarian pathology as often these lesions will be small and the affected ovary within the expected normal limit for size.(Aminimoghaddam et al., 2012; Klimek et al., 2020; Patidar et al., 2019; Suturina et al., 2022; Zaman and Rothman, 2021; Munn et al., 2022) In cases where the origin of androgen is difficult to identify, venous sampling should be performed on both the adrenal and ovarian veins to determine if there is a hormonally-active lesion in either of these structures.(Bailey et al., 2012; Klimek et al., 2020; Zaman and Rothman, 2021) Though pure Leydig cell tumors have not been shown in the literature to have malignant potential, the virilizing effects of the excess androgens can be extremely distressing to patients(Kozan et al., 2014; Staats and Young, 2019) and may not be fully reversible. Although the incidence of bilateral Leydig tumor cannot be said with certainty due to overall rarity, bilaterality has been reported multiple times in case reports(Sanz et al., 2006; Shakir et al., 2021; Hussain et al., 2021; Langevin et al., 2020), and therefore bilateral oophorectomy in postmenopausal women suspected of having a Leydig cell tumor should be considered even if the ovaries do not appear enlarged in preoperative imaging and the intraoperative findings suggest unilateral disease.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

This study did not receive any specific grant from funding agencies in public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Thomas F Chavez: Writing – original draft, Writing – review & editing, Investigation. **Minita Singh:** Writing – review & editing, Investigation. **Vaidehi Avadhani:** Writing – review & editing, Visualization, Investigation, Formal analysis, Data curation. **Regina Leonis:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

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