An Ovarian Leydig Cell Tumour in a Postmenopausal Woman that was Missed on an Ultrasonogram: A Case Report

XiaoDan Zhu
Zhejiang University School of Medicine First Affiliated Hospital
QiHan You
Zhejiang University School of Medicine First Affiliated Hospital
LinYu Zhou
Zhejiang University School of Medicine First Affiliated Hospital
Jian Jiang
Zhejiang University School of Medicine First Affiliated Hospital
TianAn Jiang (tiananjiang@zju.edu.cn)
Zhejiang University https://orcid.org/0000-0002-7672-8394

Case report

Keywords: Leydig Cell Tumour (LCT), Hyperandrogenism, Postmenopausal Women, Transvaginal Ultrasound (TVS), Contrast-enhanced Ultrasound (CEUS).

Posted Date: March 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-17455/v1

Abstract

Background:

Ovarian Leydig cell tumour (OLCT) is a rare functioning ovarian sex cord-stromal tumour (OSCST) that can cause hyperandrogenism and virilization. Its clinical and imaging features are atypical, which leads to misdiagnosis, missed diagnosis, or overtreatment.

Case presentation:

We report a case of OLCT in a postmenopausal woman that was missed on transvaginal ultrasound (TVS). Both enhanced pelvic computed tomography (CT) and magnetic resonance imaging (MRI) indicated a right adnexal space-occupying lesion.We present this missed-diagnosis case and review the literature on OLCT.

Conclusions:

When patients develop hyperandrogens, we should consider this rare disease in addition to more common causes. Contrast-enhanced ultrasound (CEUS) of the ovary could contribute to differential diagnosis when tiny tumours are not detected by imaging examinations or the diagnosis remains uncertain.

Introduction

Ovarian testicular stromal tumour, also known as a Leydig cell tumour (LCT), is a rare steroid cell tumour that accounts for less than 0.1% of all ovarian tumours [1] and is the most common tumour that causes hyperandrogenism. According to the World Health Organization (WHO) classification from 2014, steroid cell tumours are subdivided into steroid cell tumour not otherwise specified (SCT-NOS) and LCT, and most steroid cell tumours are SCT-NOS [2]. LCT is extremely rare and is mainly seen in menopausal women. The tumour is usually benign, unilateral, tiny, and solid [3]. The onset of this tumour is asymptomatic and its clinical manifestations are also atypical. Since it is extremely rare, only case studies have been reported. which leads to misdiagnosis, missed diagnosis, or overtreatment. Here, we report a case of ovarian LCT (OLCT) in a postmenopausal woman that was missed on ultrasonography, review the literature, and discuss the cause of missed diagnosis and its clinical and imaging features .

Case Presentation

A 60-year-old female at 7 years after menopause had progressive hirsutism for 6 months before admission to our hospital. She reported beard growth and significant hair growth on the pubic and groin areas for 6 months without obvious inducers. She had no other masculinity. The patient had diabetes for 2 years and was treated with metformin (0.5 g Bid) and glimepiride tablets (2 mg Qd). Serum sex hormone results were as follows: testosterone 190.4 ng/dl, dehydroepiandrosterone sulphate (DHEAS)

114.6 μg/dl, oestradiol 51 pg/ml, follicle stimulating hormone (FSH) 22.9 mIU/ml, luteinizing hormone (LH) 9.91 mIU/ml, prolactin (PRL) 4.4 ng/ml and progesterone 0.49 ng/ml. The medium-dose dexamethasone suppression test (DST) results were follows: before and after the DST, her androstenedione levels were 3.7 ng/ml and 1.6 ng/ml, her testosterone levels were 504.5 and 244.7 ng/dl, and her DHEAS levels were 65.5 μg/dl and 42.1 μg/dl, respectively. Her 17α-hydroxyprogesterone level was 0.1 nmol/L after DST. Adrenal CT scan showed no obvious abnormalities. Pelvic CT scan displayed a right adnexal nodule that intensified after enhancement (Fig. A). Pelvic MRI revealed a nodular lesion with high intensity on T2W1 and DW1 in the right adnexa (Fig. B). TVS revealed uterine atrophy accompanied by uterine fibroids and multiple cervical cysts, but no space-occupying lesion was observed in adnexal areas in multiple scans.

The patient then underwent total hysterectomy + bilateral adnexectomy. A solid mass of 2 cm, with medullary components inside, was detected during surgery. A 1.7 cm grey-white nodule was seen on a section of the mass. The section stained for pathologic analysis favoured LCT (Fig. C): Calretinin (CR) (+), CgA(-), CK(pan) (+), Inhibin a(+), Ki-67 (6%), S-100(-), CD99(-), SMA(-). The testosterone level had decreased to 57.1 ng/dl one day after surgery and was normal at re-examination.

Discussion

OSCST is the most common cause of hyperandrogenism, which leads to various virilization symptoms, including progressive hirsutism, acne, hoarseness, amenorrhea, breast atrophy, and male-type baldness [4]. Both ovarian and adrenal lesions can cause hyperandrogenism. Sexual cord-stromal tumors are the most common ovarian functional tumors that cause hyperandrogenemia. Hyperandrogenism caused by adrenal tumours is due to the secretion of DHEAS, while LCT primarily secretes testosterone [5]. The average age of onset of adrenal tumours that cause hyperandrogenism is 58 years, but these tumours can also occur in children and women aged 40–50 years [6]. The adrenal tumours are usually large and invasive, progress rapidly, and are fatal when accompanied by Cushing syndrome [7]. When a postmenopausal women suddenly exhibit a gradual rise in androgens and normal dehydroepiandrosterone levels, we should strongly suspect that their androgens originate from functional ovarian tumours.

Some functioning ovarian tumours, such as LCT, SCT-NOS, and mature teratomas, can cause hyperandrogenism. Of these, LCT is most frequently found in postmenopausal women and accounts for less than 0.1% of all ovarian tumours. Androgen-producing Leydig cells are present in the ovaries of more than 80% of women [8]. The age at onset of SCT-NOS ranges from 3 to 93 years, with a mean age at diagnosis of 47 years [9]. Its clinical manifestations are determined by the steroid hormone produced by the tumour[10–11]. In most patients (56–77%), the tumour secretes testosterone and causes virilization. Excessive oestrogen was seen in 6% of patients, which leads to menorrhagia or postmenopausal bleeding and eventually to endometrioid adenocarcinoma. Approximately 25% of SCT-NOS tumours do not produce any hormones. Mature teratoma is the most common germ cell tumour, but it does not

frequently cause hyperandrogenism. In most cases, mature teratoma contains non-secretive tissue and rarely produces testosterone-induced virilization [12–13].

Certain scholars believe that imaging studies are not helpful for the detection and diagnosis of small ovarian tumours. Hofland [8] believes that even negative imaging test results cannot exclude the existence of LCT or Leydig cell hyperplasia. He reported a case of Leydig's hyperplasia for which both MRI and ultrasound showed normal ovarian size, with enhanced perfusion only in the left ovary. However, postoperative pathology confirmed bilateral proliferation of ovarian Leydig cells. Palha [14] believes that because LCTs are extremely small, these ovarian tumours lack typical imaging features and there is a lack of diagnostic consistency between imaging and histology. Of the 3 cases of LCT she discussed (all of which involved tumours smaller than 3 cm), 2 cases included negative ultrasound and CT results. In the remaining case, ultrasound and CT only showed bilateral ovarian enlargement, but surgery confirmed LCT in the left ovary.

TVS is the first choice for imaging and diagnosis of ovarian tumours due to its convenience, speed, and non-invasiveness. But TVS for LCT in postmenopausal women is still challenging. First, almost all LCTs are less than 5 cm in diameter [15]. Small LCTs (usually < 3 cm) may be invisible on ultrasound and CT scans [12]. Secondly, it can be divided into leydig cell hyperplasia (< 1 cm) and LCT (> 1 cm) according to the difference in size and growth pattern, and because the hyperplasia is usually widely nodular, it is difficult to distinguish them[16–17]. Besides, due to decreased oestrogen level and insufficient ovarian arterial blood flow, ovaries shrink rapidly in menopausal women, the thin cortex and the altered cortex-to-medulla ratio cause the ovary to appear solid and hyperechoic; on colour Doppler flow imaging (CDFI), with no blood flow visible [18]. TVS in this case showed uterine and ovarian atrophy. The ovaries were significantly small and slightly hypoechoic, with diameters of approximately 2.13 cm (right) and 2.0 cm (left), but no obvious space-occupying lesions were detected in the adnexal areas and no obvious blood flow signal in CDFI. Postoperative, the stored images were re-examined and a slightly hyperechogenic nodular lesion (1.23 cm)was found in the right ovary (Fig. D). The boundary between nodule and peripheral atrophic ovarian tissue was unclear. Combined with pelvic enhanced CT and MRI images as well as surgical and pathological findings, we concluded that the slightly hyperechogenic nodular lesion in the right ovary was LCT, which was previously not diagnosed. In summary, an ovarian tumour with a diameter of more than 1 cm but less than 3 cm may exhibit poor visibility on ultrasound examination. Additionally, when LCTs show a slightly hypoechogenic[19] or hyperechogenic nodule may lack a sharp boundary with the surrounding atrophic ovarian tissue; thus, ultrasound physicians who have little experience with LCTs can easily treat lesions as part of the atrophic ovarian tissue, potentially causing false-negative ultrasound results and leading to missed diagnoses.

Demidov et al. [20] reported 5 cases of LCT, all of which were solid and small. They found that moderate or high blood flow signals could be seen in CDFI of these tumours. In this case, the intensification did appear in enhanced CT and MRI. Based on known imaging findings, we believe that although ovarian LCTs are difficult to distinguish from normal atrophic ovarian tissue in postmenopausal women, blood

flow signals in the tumour on CDFI and enhanced perfusion in the tumour on CT or MRI may be used to identify ovarian LCT and reveal important imaging features of atrophic ovarian tissue. Given the principles of CEUS [21], we believe that CEUS of the ovary may be helpful for distinguishing between atrophic ovarian tissue and small ovarian tumours and for understanding the microcirculatory perfusion status of lesions. We performed a CEUS of ovarian in a case involving a suspected hyperechoic lesion in the ovary of an elderly woman at 10 years after menopause. In this patient, a suspicious lesion of approximately 1 cm in size was found in the left ovary on TVS. The boundary between the lesion and atrophic ovarian tissue was not clear. CDFI showed little blood flow signal in the lesion(Fig. E). Enhanced CT showed no abnormal ovaries. We injected 2.4 ml of contrast agent (Sono Vue) through peripheral blood vessels. Real-time TVS observation showed that the intra-ovarian lesion rapidly increased in the arterial phase and subsided significantly in the late phase. The boundary between the lesion and the surrounding atrophic ovarian tissue was extremely clear. Using CEUS, we definitively established that the patient had a small tumour in the left ovary and unimpeded blood supply (Fig. F). The patient's sex hormone levels did not show abnormal changes. Postoperative pathology suggesting that the lesion was a mature teratoma. Based on this examination, we believe that CEUS can help us distinguish between atrophic ovarian tissue and small ovarian tumours in postmenopausal women and understand the microcirculation perfusion status of lesions. CEUS is especially advantageous for assessing tumours with an approximate diameter of only 1 cm, while CDFI does not show rich blood flow signals; for such tumours, this technique can be the most beneficial for avoiding imaging misdiagnosis. Moreover, when combined with consideration of the patient's clinical manifestations and changes in hormone levels, CEUS will greatly facilitate the clinical diagnosis of postmenopausal ovarian LCT.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publish

Written informed consent was obtained from the patient for publication of this Images in

article and any accompanying images.

Availability of data and materials

All the data supporting our findings are contained within the manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

The authors declare that they have no funding support.

Authors' contributions

XDZ drafted the manuscript, collected the data, and reviewed the literature. LYZ and JJ performed the histological examination and reviewed the manuscript. QHY offered pathological help. NO critically reviewed the manuscript. All authors confirmed and approved the final manuscript.

Acknowledgements

The authors thank Dr.LinYu Zhou, Dr.Jian Jiang and Dr.QinHan You for helpful advice and Professor TianAn Jiang of the Ultrasound Medicine Department for discussion and manuscript revision.

Abbreviations

Steroid cell tumour; not otherwise specified: SCT – NOS; LCT: Leydig cell tumour; MRI: magnetic resonance imaging; CT: computed tomography; TVS: transvaginal ultrasound; CEUS□contrast-enhanced ultrasound .

References

1. Swain J, Sharma S, Prakash V, et a1. Steroid cell tumor: a rare cause of hirsutism in a female[J]. Endocrinol Diabetes Metab Case Rep, 2013, 2013(2013) 13003.
2. Wang Jing, Wu Huanwen, Liang Zhiyong. Clinical analysis of 19 cases of ovarian steroid cell tumor [J]. J Diagnostic Pathol, 2017, 8(24): 561 -569.
3. Freitas ACL, Lima J, Pessoa J, et al. Leydig cell tumor of the ovary-a case report. Revista da Faculdade de Ciências Médicas de Sorocaba.2014; 16: 152–4.
4. Sood N, Desai K, Chindris AM, et al. Symptomatic Ovarian Steroid Cell Tumor not Otherwise Specified in a Post-Menopausal Woman [J]. Rare Tumors, 2016, 8(20): 6200.
5. Burger HG. Androgen production in women. [J] Fertil Steril, 2002, 77(4): S3-5.
6. Ng L, Libeaino, JM. Adrenocortical carcinoma: diagnosis, evaluation and treatment [J]. J Urol, 2003, 169(1): 5-11.
7. Azziz R, Carmina E, Dewailly D, et a1. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report [J]. Fertility and Sterility, 2009, 91(2): 456-488.
8. Maarten Hofland, Stef Cosyns, Philippe De Sutter, et al. Leydig cell hyperplasia and Leydig cell tumor in postmenopausal women: report of two cases. Gynecological Endocrinology, 2013; 29(3): 213–215.
9. Wan J, Chen X, Li X. Ovarian steroid cell tumor, not otherwise specified: A rare case of postmenopausal vaginal bleeding [J]. Oncol Lett, 2014(3): 1187-1189.

10. Hayes MC, Scully RE. Ovarian steroid cell tumors (not otherwise specified). A clinicopathological analysis of 63 cases [J]. Am J Surg Pathol, 1987, 11(11): 835-845.
11. Lee J, John VS, Liang SX, et al. Metastatic Malignant Ovarian Steroid Cell Tumor: A Case Report and Review of the Literature [J]. Case Rep Obstet Gynecol, 2016, 2016: 6184573.
12. Shanbhogue AKP, Shanbhogue DKP, Prasad SR, et al. Clinical syndromes associated with ovarian neoplasms: a comprehensive review. Radiographics 2010; 30: 903–19.
13. Hoffman JG, Strickland JL, Yin J. Virilizing ovarian dermoid cyst with leydig cells. J Pediatr Adolesc Gynecol 2009; 22: e39–40.
14. Ana Palha, Luísa Cortez, Ana Paula Tavares, Ana Agapito. Leydig cell tumor and mature ovarian teratoma: rare androgen-secreting ovarian tumors in postmenopausal women. BMJ Case Rep 2016. doi: 10.1136/bcr-2016-215985.
15. Nardo LG, Ray DW, Laing I, et al. Ovarian Leydig cell tumor in a peri-menopausal woman with severe hyperandrogenism and virilization. Gynecol Endocrinol 2005; 21: 238–41.
16. Robboy SJ, Anderson MC, Russel P. Pathology of the Female Reproductive Tract, Toronto: Churchill Livingstone; 2002. p 511.
17. Scully RE, Young RH, Clement PB. Atlas of tumor pathology: Tumors of the ovary, maldeveloped gonads; fallopian tube and broad ligament, third series. Washington: Armed Forces Institute of Pathology; 1998. p 421.
18. Sarfati J, Bachelot A, Coussieu C, et al. Study Group Hyperandrogenism in Postmenopausal Women. Impact of clinical, hormonal, radiological, and immunohistochemical studies on the diagnosis of postmenopausal hyperandrogenism. Eur J Endocrinol 2011; 165: 779–88.
19. Wang L, Ma X, Luo J, et al. Study on the correlation between ovarian size and the use of vasodilator in menopause by imaging techniques. Journal of Medical Imaging Vol.19 No.5 2009.
20. Demidov VN, Lipatenkova J, Vikhareva O, et al. Imaging of gynecological disease(2): clinical and ultrasound characteristics of Sertoli cell tumors, Sertoli–Leydig cell tumors and Leydig cell tumors. Ultrasound Obstet Gynecol 2008; 31: 85–91.
21. Chen L. Behaviors of contrast agents in the ultrasound field and emerging contrast imaging [J]. Foreign Medical Sciences (Biomedical Engineering Fascicle) 2004, 27(3): 188-192.

Figures

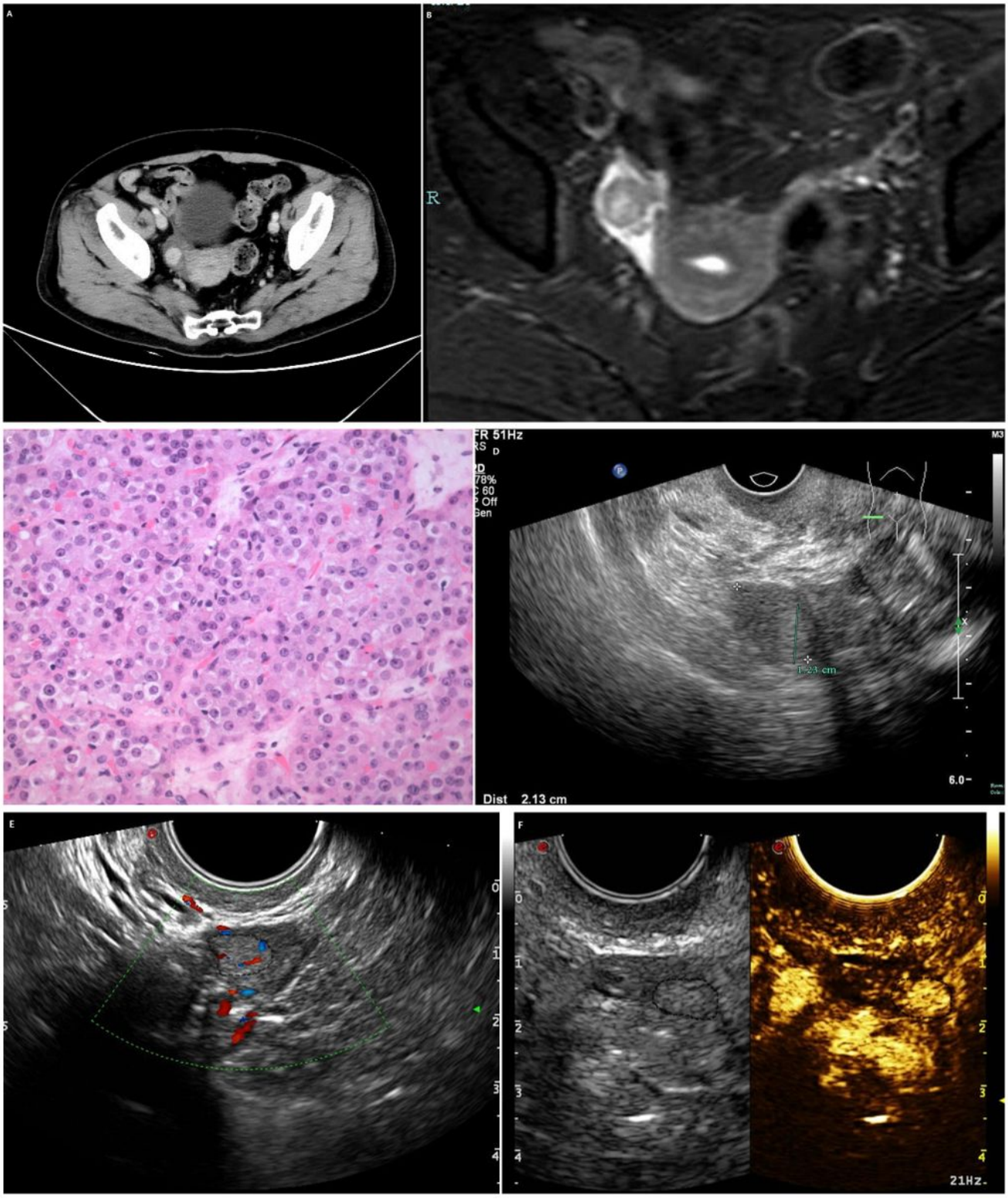

Figure 1

A: Enhanced CT showed a nodular lesion with slightly increased signal intensity in the right adnexa, which was intensified after enhancement. B: Pelvic MRI showed an oval-shaped lesion with abnormal signal intensity in the right adnexa. C: Haematoxylin-eosin staining by microscopy, magnification 400x (C). D: Slightly hyperechogenic lesion with less clear boundary and a diameter of 1.23 cm in the right atrophic ovary. E: Slightly altered echogenic foci with diameters of approximately 1.1 cm can be seen in

the atrophic tissue of the left ovary with changes in solidity; the border is unclear. F: Contrast-enhanced ultrasound showed rapid, strong enhancement of the lesion in the arterial phase.