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CASE REPORT

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Rare case of occult testosterone-producing ovarian tumor that was diagnosed by selective venous hormone sampling

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Abstract

Case: A 32 year old woman was referred because of secondary amenorrhea, hirsutism, and voice deepening.

Outcome: The blood testosterone level was markedly high. A transvaginal ultrasound revealed a small region in the left ovary, but whether or not it was a tumor was unclear. Therefore, selective ovarian venous sampling was performed. Consequently, the testosterone level was selectively increased in a blood sample that was taken from the left ovarian vein, the tumor was successfully localized, and a laparoscopic left oophorectomy was performed. Although the left ovary appeared to be normal at laparoscopy, the androgen-secreting tumor was located within it. The tumor was diagnosed as a Leydig cell tumor by histopathological analyses.

Conclusion: This report demonstrates that selective blood sampling from ovarian veins before an operation is effective in localizing an androgen-producing ovarian tumor that is difficult to diagnose by imaging studies.

KEYWORDS

diffusion-weighted imaging, Leydig cell tumor, ovary, selective venous blood sampling, testosterone

1 | INTRODUCTION

Hyperandrogenism is one of the most common endocrine disorders in women of reproductive age, causing menstrual disorder, acne, hirsutism, and virilization. A wide variety of disorders can be the source of excess androgen. Functional hyperandrogenism, such as polycystic ovary syndrome and theca cell hypersensitivity related to luteinizing hormone, is relatively common. Although androgen-secreting tumors in the gonadal or adrenal gland are rare, they should be considered as differential diagnoses. Imaging procedures, including pelvic ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), are helpful in localizing the tumor before the operation. However, it is sometimes difficult to localize androgen-secreting tumors because of their small size. If a CT or MRI cannot clearly identify a tumor, selective venous hormone sampling (SVHS) can be the next option. Here is reported a case of a testosterone-producing tumor of the ovary that was localized by SVHS.

2 | CASE REPORT

A 32 year old woman (gravid: 0, para: 0) was referred because of secondary amenorrhea, hirsutism, and voice deepening. Her first menstruation was at the age of 13 years and her menstrual cycle was irregular. She developed amenorrhea at the age of 28 years with hirsutism, clitoromegaly, and acne. She noticed voice deepening 2 years ahead of the amenorrhea. At physical examination, her height was 164 cm and her body weight was 56 kg (body mass

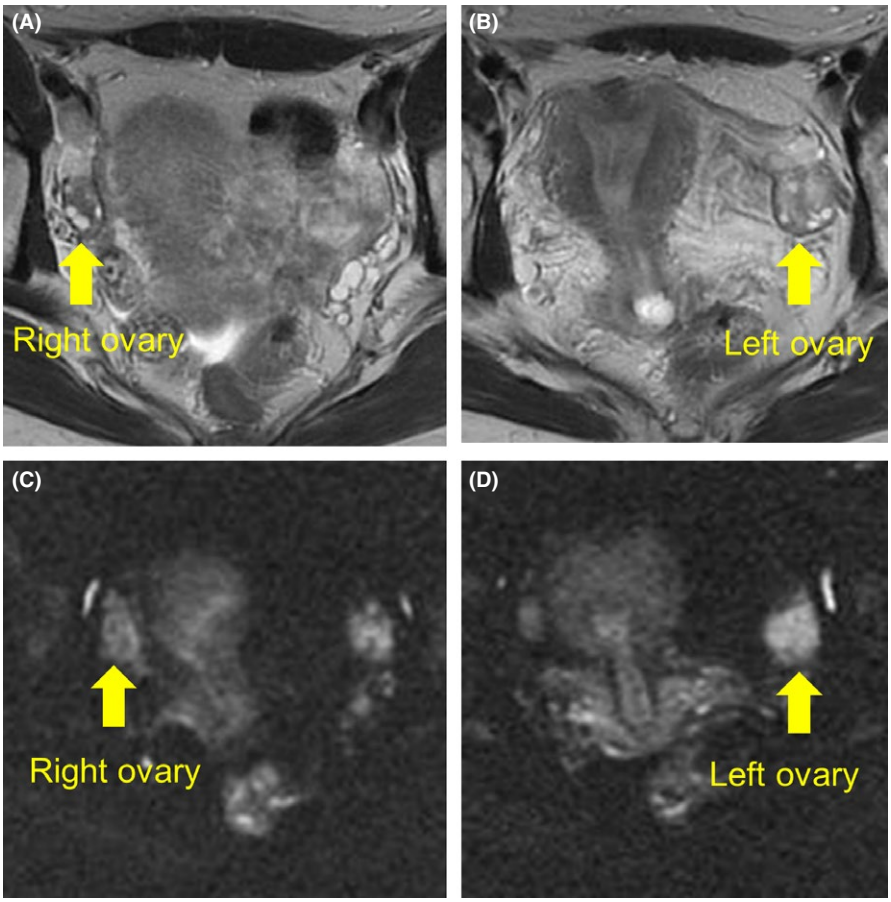

FIGURE 1 Magnetic resonance imaging of the ovaries. A and B, T2-weighted images. C and D, Diffusion-weighted images. The left ovary had a higher intensity area than that of the right ovary

index: 20.8 kg/m^2). Her gynecological examination was negative, except for clitoromegaly. Hirsutism was not observed because of hair removal. A transrectal ultrasound showed 3 mm endometrial thickness. The left ovary was slightly bigger than the right ovary, but neither color Doppler flow nor a tumor was detected. A tumor was not detected in the adnexa, adrenal glands, or other body parts on CT and MRI. However, the diffusion-weighted image (DWI) showed a slightly higher signal in the left ovary than that in the right one (Figure 1). The measurements of the circulating hormones revealed severe hyperandrogenism, with a testosterone level of 8.24 ng/mL (normal range: 0.11-0.47), but androstenedione and dehydroepiandrosterone sulfate (DHEA-S) were within their normal range. The luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were slightly suppressed (Table 1). The red blood cell count, hemoglobin, and hematocrit levels were above the normal upper limit. The ovarian tumor markers were within their normal range, except for squamous cell carcinoma (SCC) (Table 1). The result of the chromosomal analysis was 46, XX.

Despite virilization and elevated testosterone, neither the CT nor the MRI showed an apparent tumor. Therefore, we treated the patient with anti-androgen (spironolactone), a low-to-medium dose of the pill, an insulin-sensitizing drug, and a gonadotropin-releasing hormone agonist against hypertestosterone. Furthermore, clomiphene (100 mg/d for 5 days) was tried for the amenorrhea. Although follicular development and an ovulation-like finding were observed in the ultrasound, menstruation did not occur. As the above treatment was not effective at reducing the testosterone level, the bilateral ovaries were reevaluated by a transrectal pelvic ultrasound and a high echogenic area of 17 mm in diameter was found on the left ovary.

In order to confirm the presence of the suspected tumor and to localize it, the SVHS was carried out. A catheter was inserted into the femoral vein and blood samples from the bilateral ovarian veins and the inferior vena cava were collected in order to measure the testosterone concentration, which was markedly higher in the blood sample that was taken from the left ovarian vein than that from the right ovarian vein and inferior vena cava. Based on these results, a left ovarian androgen-producing tumor was diagnosed (Figure 2, Table 2).

Finally, a laparoscopic left oophorectomy was performed, which allowed for the identification of a 20 mm ovarian tumor within the ovary. The left ovary was 32 mm × 26 mm × 19 mm, which macroscopically seemed to be normal, with a smooth-looking surface. On a cut surface, a sharply circumscribed tumor was seen, with a grayish-white color (Figure 3). The pathologic diagnosis was a Brenner tumor and Leydig cell tumor that had been immunostained with inhibin α, calretinin, and vimentin. Supporting the diagnosis, rod-shaped crystalloids (Reinke crystalloids) were observed within cellular clusters (Figure 4).

The blood testosterone level decreased after the tumor removal and the LH and FSH increased rapidly. The patient's regular menstrual cycle was restored 43 days after the operation. In addition,

TABLE 1 Laboratory parameters before and after surgical treatment

Variable	The first visit	2 months before operation	Operation	2 months after operation	Normal range
Testosterone (ng/mL)	8.24	12.50	–	0.15	0.11-0.47
Androstenedione (ng/mL)	0.37	1.56	–	0.67	0.57-2.24
DHEA-S (μg/dL)	185.00	258.00	–	–	23.00-266.00
LH (mIU/mL)	2.10	1.87	–	5.27	–
FSH (mIU/mL)	2.28	2.77	–	6.45	–
Estradiol (pg/mL)	27.98	133.60	–	<5.00	–
ACTH (ng/mL)	20.20	13.70	–	–	7.20-63.30
Cortisol (μg/dL)	12.50	–	–	–	4.00-18.30
Prolactin (ng/mL)	14.56	–	–	–	4.90-29.30
AMH (ng/mL)	5.60	–	–	5.32	–
WBCs (/μL)	3900.00	4000.00	–	4700.00	3500.00-9000.00
RBCs ($\times 10^6$/μL)	5.13	5.34	–	4.65	3.80-5.00
Hemoglobin (g/dL)	15.60	16.20	–	13.70	11.10-15.10
Hematocrit (%)	45.60	48.80	–	42.40	33.50-45.00
Platelets ($\times 10^4$/μL)	18.20	17.10	–	19.90	13.20-36.80
SCC (ng/mL)	2.00	2.90	–	1.00	.00-1.50
CA19-9 (U/mL)	5.00	–	–	–	.00-37.00
CA125 (U/mL)	9.80	–	–	–	1.00-35.00
AFP (ng/mL)	1.90	–	–	–	.00-8.50

ACTH, adrenocorticotropic hormone; AFP, alpha-fetoprotein; AMH, anti-Müllerian hormone; CA, cancer antigen; DHEA-S, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; RBC, red blood cell; SCC, squamous cell carcinoma; WBC, white blood cell.

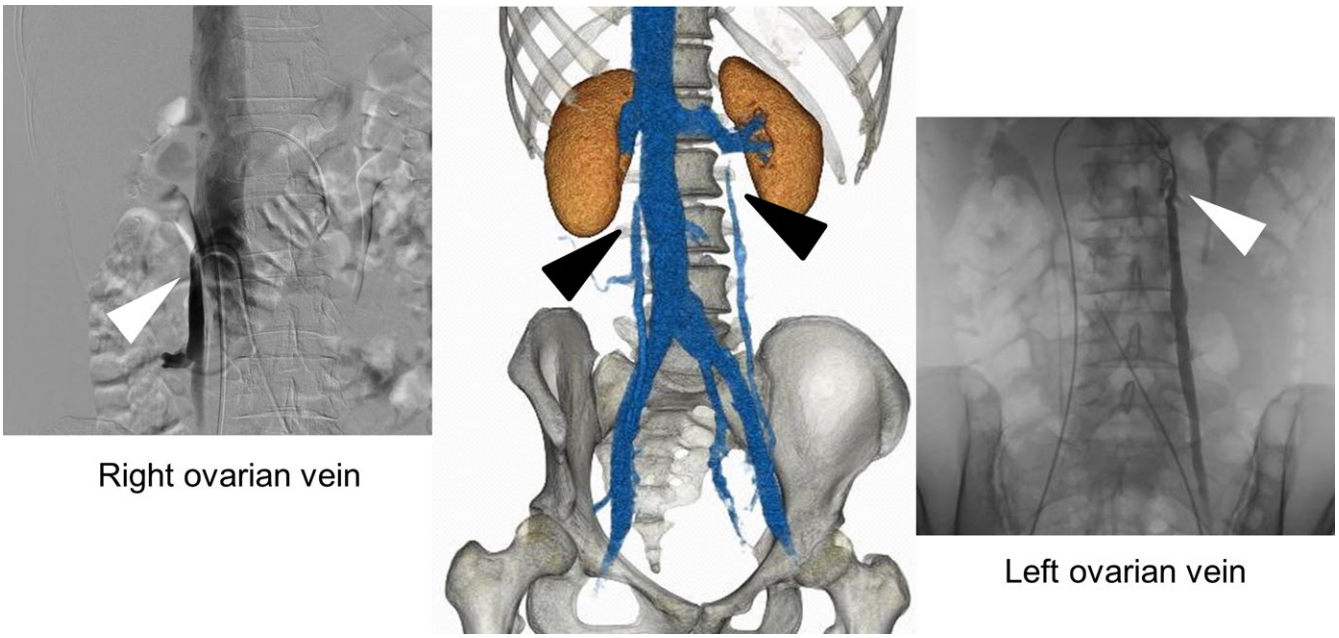

FIGURE 2 Selective ovarian venous sampling. (Center panel) Three-dimensional images of the ovarian veins (black arrowheads). (Left and right panels) Angiographic images of the ovarian veins and sampling points (white arrowheads)

the erythrocytosis resolved (Table 1). At 11 months after surgery, the patient did not show evidence of recurrence. Her body weight had decreased by 2 kg during the 2 months postoperation. Acne and hirsutism on the upper arm were reduced, but the beard, clitoromegaly, and deepening of the voice were sustained. On the ultrasound examination, the polycystic ovary form was unchanged.

TABLE 2 Selective venous catheterization and hormonal sampling

Vein	Testosterone level (ng/mL)
Right ovarian vein	10.66
Left ovarian vein	154.50
Inferior vena cava	10.43
Peripheral vein	10.52
Normal range (peripheral blood)	0.11-0.47

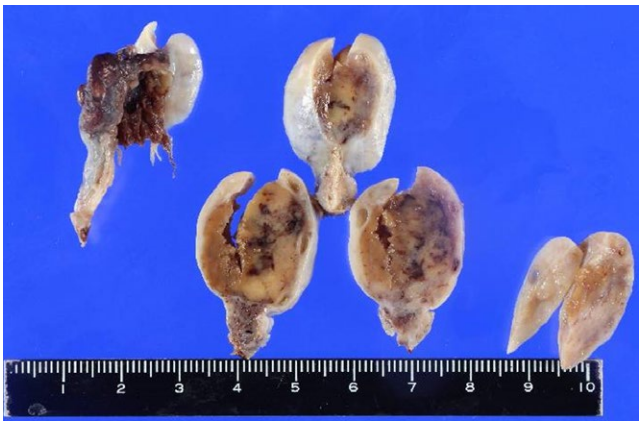

FIGURE 3 Cut sections of the left ovary, which contained a 20 mm × 20 mm grayish-white, soft nodule

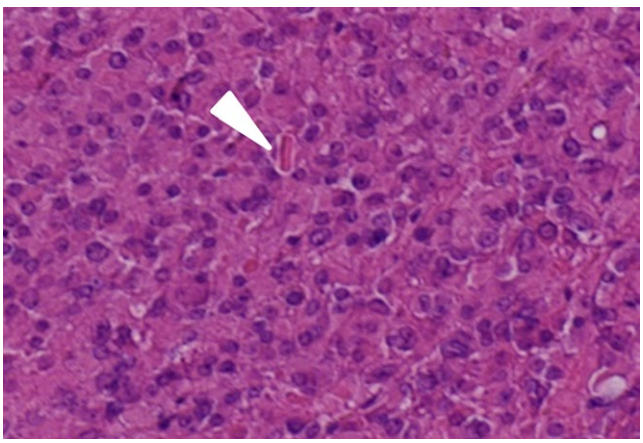

FIGURE 4 Hematoxylin and eosin staining of the ovarian tumor, which was composed of cells with round nuclei and an eosinophilic cytoplasm. An arrowhead indicates the Reinke crystalloid

3 | DISCUSSION

The major circulating androgens, including DHEA-S, DHEA, androstenedione, testosterone, and dihydrotestosterone, are mainly secreted by the ovaries and adrenal glands. Testosterone is thought to be equally produced by both the ovaries and adrenal glands. Therefore, a thorough examination of the ovaries and adrenal glands is necessary when excess levels of testosterone are observed. In the present case, the serum testosterone level was extremely high and was almost the same as those in men. In addition, the gonadotropin levels were within the normal range. These findings often are seen in cases of female-to-male transsexualism with exogenous testosterone administration. Therefore, it was first considered that testosterone-secreting tumors probably can be compared to functional hyperandrogenism. However, the first check-ups using a CT and MRI failed to identify the tumor. As a result, SVHS was performed.

Leydig cell tumors are rare and typically occur in postmenopausal women. They account for 0.1% of ovarian tumors and are usually unilateral and benign.[1] They cause hirsutism and virilization in 75% of cases.[1] In addition, the Leydig cell tumors that are found in ~10%–20% of women are associated with some degree of estrogenic effect, such as endometrial hyperplasia.[1-3] They can be large and have a multifocal neoplasm. However, in many cases, detecting these tumors by uninvasive imaging techniques is challenging because they are often small and unilateral.[4] In such a case, transvaginal color Doppler studies,[5] selective catheterization,[6] and fluorodeoxyglucose-positron emission tomography or CT scans have been reported to raise the ability to detect an androgen-secreting tumor.[7,8] In this case, SVHS can be very informative. However, some potential technical difficulties exist, including catheterization to the right ovarian vein due to anatomical issues.[9] The success rate of sampling from all adrenal and ovarian veins is only 27%-45%[10-12] and rupture of the ovarian vein during sampling is one potentially serious complication by SVHS. Therefore, this should be considered when other imaging and diagnostic studies are not helpful in tumor localization.[6]

Erythrocytosis improved after the oophorectomy, suggesting the involvement of testosterone in erythrocytosis. Previous reports have shown that androgen leads to an increase in the production of erythropoietin,[13,14] acts synergistically with erythropoietin on committed erythroid cells,[15,16] enhances the survival of mature erythrocytes via a direct action on the erythropoietic stem cells,[17] and increases iron bioavailability.[18] Therefore, androgen should be measured in women with unexplained erythrocytosis.[1]

Pure SCC of the ovary is rare. The blood level of a SCC can be increased in a mature teratoma, ovarian endometriosis, or Brenner tumor.[19] As this case was caused by a Leydig cell tumor that was associated with a Brenner tumor, it is possible that the increase in the SCC level was related to the Brenner tumor.

In this case, it was chosen to perform a laparoscopic oophorectomy because the precise localization of the tumor in the ovary was obscure in a macroscopic finding and the tumor might have been malignant. However, the size of the tumor did not change over several months and malignancy was unlikely. When the occult tumor is found by SVHS, tumor enucleation would be the option of choice. Retrospectively, a suggestive tumor was found on an image of the DWI, which has a high ability to pick up lesions; therefore, it might assist to detect a small tumor before SVHS and reduce the invasiveness of searching all veins of the ovaries and adrenal glands. The SVHS gives more reliable evidence to decide on whether an operation is needed, but the DWI might be useful

in a facility where SVHS is not readily available. In such a facility, laparoscopic venous sampling[20] might be one clue to diagnose a small tumor.

DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human rights statement and informed consent:* The authors obtained signed consent from the patient to publish the information. *Animal studies:* This article does not contain any studies with animal participants that have been performed by any of the authors.

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