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Detection of pure Leydig cell ovarian tumor not visible on imaging by selective venous blood sampling in a woman with secondary amenorrhea and hirsutism: A case report

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ABSTRACT

A 39-year-old woman (gravida 1, para 1) was referred to a university hospital with a high serum testosterone level and secondary amenorrhea, hirsutism, and weight gain. Her voice was deep, and hirsutism was observed on her chin, arms, and back. She also had clitoromegaly. Her serum testosterone levels were markedly elevated (testosterone 11.1 ng/mL, free testosterone 15.5 pg/mL). Transvaginal ultrasonography and magnetic resonance imaging did not reveal any tumors in the pelvic organs, including the uterus and ovaries. Enhanced computed tomography revealed no abnormalities in either adrenal gland. Blood sampling from the inferior vena cava, left renal vein, and the ovarian veins on both sides revealed an extremely high testosterone level (391 ng/mL) in blood from the right ovarian vein. Laparoscopic right oophorectomy was performed and the pathologic diagnosis was a Leydig cell tumor (1.5 × 1.5 × 1.3 cm). Her serum testosterone level decreased rapidly following oophorectomy (0.3 ng/mL on postoperative day 2). Her menstrual cycle had recovered spontaneously by 2 months after surgery and she noticed improvement in the hirsutism 4 months after the operation.

1. Introduction

Hirsutism is a common complaint and a significant concern in women with androgen excess. Sertoli–Leydig ovarian tumors are the most common sex cord-stromal androgen-producing tumors but represent less than 0.5% of ovarian neoplasms in humans [1]. Although Sertoli–Leydig cell tumors contain heterologous elements, pure Sertoli cell tumors, which are usually estrogenic, and pure Leydig cell tumors, which are usually androgen-secreting, have also been observed [2,3]. A Sertoli–Leydig cell tumor may be suspected if symptoms of virilization are observed or there is a high plasma testosterone level [1]. In most cases, conventional radiologic imaging can detect Sertoli–Leydig cell tumors when the tumor mass reaches a significant size. However, if the tumor is too small to detect by diagnostic imaging, it is difficult to make a differential diagnosis before surgery. Here we report a case of Leydig cell tumor that was undetectable on imaging, the localization of which was predicted by selective venous blood sampling.

2. Case Presentation

A 39-year old woman (para 2, gravida 2) was referred to a university hospital for investigation of hirsutism and high serum testosterone levels. Although her menstrual cycle was originally regular, she had started taking a low-dose estrogen–progestin combination 6 years earlier for irregular menstruation. Three years later, she changed to drospirenone–ethinyl estradiol combination tablets after noticing hypertrichosis and weight gain. She had sought an extended prescription from her previous doctor because she was changing her place of residence. The doctor performed a routine laboratory examination, which revealed extremely high serum testosterone levels. When she visited the hospital, she was most concerned about her hirsutism. She was centrally obese with a body mass index of 31.6. Physical examination revealed prominent hirsutism on her chin, arms, abdomen, and back. Her Ferriman-Gallwey score was 22 (a score ≥ 8 indicates generalized hirsutism) [4]. Furthermore, she felt her voice was deeper than before. There was no palpable mass on bimanual pelvic examination. Her clitoris was significantly enlarged. A transvaginal sonogram showed that both ovaries were of normal size with no detectable ovarian masses. There was no sign of polycystic ovarian syndrome.

Her blood test results are shown in Table 1. Biochemical investigations, including liver and renal function, were unremarkable. However, her red cell count, hemoglobin level, and hematocrit seemed to be slightly high for a woman. Endocrine examination revealed severe hyperandrogenism with a total testosterone concentration of 1.1 ng/mL (reference value 0.11–0.47 ng/mL) and a free testosterone concentration of 15.5 pg/mL (reference value 0.9–0.25 pg/mL). The dehydroepiandrosterone sulfate level was within the normal range. The serum level of estradiol level was extremely low (19 pg/mL; reference

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Table 1
Results of laboratory investigations.

WBC	5100/μL	LDH	123 U/L
RBC	5.63×10^6/μL	BUN	12.7 mg/mL
Hgb	14.1 g/dL	Crea	0.66 mg/dL
Hct	44.0%	Na	140 mEq/L
Plt	250×10^3/μL	K	4.2 mEq/L
TP	6.9 g/dL	Cl	106 mEq/L
Alb	3.6 g/dL	T-Cho	218 mg/dL
AST	13 U/L	TG	93 mg/dL
ALT	11 U/L	BS	86 mg/dL
Hormonal data			
E2	19 pg/mL (≧28.8 pg/mL)	ACTH	9.0 pg/mL (7.7– 63.1 pg/mL)
LH	<0.1 mIU/mL (≧0.5 mIU/mL)	Cortisol	11.2 μg/mL (2.0– 18.0 μg/mL)
FSH	0.3 mIU/mL (≧1.5 mIU/mL)	DHEA-S	109 μg/dL (23– 266 μg/dl)
T	11.1 ng/mL (0.11–0.47 ng/mL)	Adrenaline	15 pg/mL (≦100 pg/mL)
FreeT	15.5 pg/mL (0.9–0.25 pg/mL)	Noradrenalin	208 pg/mL (100– 450 pg/mL)
PRL	16.8 ng/mL (4.1– 28.9 ng/mL)	Dopamine	9 pg/mL (≦20 pg/mL)
GH	2.6 ng/mL (< 3.0 ng/mL)	Aldosterone	186.7 pg/mL (35.7– 240 pg/mL)
FT3	4.0 pg/mL (2.1– 3.8 pg/mL)	*Dexamethasone suppression test*	
FT4	1.09 pg/mL (0.8– 1.5 pg/mL)	ACTH	<5.0 pg/mL
TSH	2.16 μU/mL (0.500– 3.000 μU/mL)	Cortisol	0.8 μg/dL
		T	9.43 ng/mL

Reference value in parentheses.
ACTH, adrenocorticotropic hormone; Alb, albumin; ALT, alanine transaminase; AST, aspartate transaminase; BG, blood glucose; BUN, blood urea nitrogen; Crea, creatinine; DHEA-S, dehydroepiandrosterone sulfate; E2, estradiol; FSH, follicle-stimulating hormone; GH, growth hormone; Hgb, hemoglobin; Hct, hematocrit; LDH, lactate dehydrogenase; LH, luteinizing hormone; Plt, platelets; PRL, prolactin; RBC, red blood cells; T, testosterone; T-Cho, total cholesterol; TG, triglycerides; TP, total protein; TSH, thyroid-stimulating hormone; WBC, white blood cells.

value ≧ 28.8 pg/mL), as were the levels of luteinizing hormone (<0.1 mIU/mL; reference value ≧ 0.5 mIU/mL) and follicle-stimulating hormone (0.3 mIU/mL; reference value ≧ 1.5 mIU/mL). Other hormones, including prolactin, growth hormone, thyroid hormones, and adrenal gland-related hormones were all within normal range. Serum adrenocorticotropic hormone and cortisol levels were strongly suppressed by the dexamethasone suppression test; however, the testosterone level remained elevated (9.43 ng/mL; Table 1).

Although a transvaginal ultrasound did not show any abnormal findings in the ovaries, further diagnostic imaging was performed. No enlargement or tumor formation was detected in the adrenal glands on abdominal enhanced computed tomography. Pelvic magnetic resonance imaging did not detect any abnormality in the pelvic organs, including both ovaries. Neither of the ovaries was polycystic.

Selective venous catheterization and hormone sampling were performed to find the origin of the excessive androgen production. Serum testosterone levels from selective sampling of the left ovarian vein, left renal vein, and superior and inferior vena cava were all high (6.62 to 7.75 ng/mL); however, venous sampling from the right ovarian vein showed a remarkably elevated serum testosterone level (391 ng/mL) compared to the levels in the other veins (Table 2).

Table 2
Serum testosterone levels based on selective venous sampling.

Sampling region	Testosterone level (ng/mL)
Right ovarian vein	391
Left ovarian vein	7.17
Left renal vein (distal from the confluence of the left ovarian vein)	6.62
Proximal side of the inferior vena cava	7.75
Distal side of the inferior vena cava	7.54

Therefore, suspecting an androgen-producing origin in the right ovary, we performed a laparoscopic right oophorectomy. Although there was a follicular cyst in the right ovary, no obvious mass lesion was observed. When the ovary was divided after the oophorectomy, a brown solid mass measuring 1.5 × 1.5 × 1.3 cm was noted at the hilum of the ovary (Fig. 1A). Microscopically, the tumor consisted of small rounded cells with rich eosinophilic cytoplasm (Fig. 1B). Some cells possessed conspicuous nucleoli or a large nucleus. There was fibrinoid degeneration of the blood vessel walls. There was hemorrhage within the tumor. The border between the tumor cells and the normal ovarian tissues was well defined. The final histological diagnosis was that of a pure Leydig cell tumor.

The postoperative course was uneventful. Her serum testosterone and free testosterone levels decreased to 0.3 ng/mL and 1.0 pg/mL 2 days after the right oophorectomy. Serum luteinizing hormone and follicle-stimulating hormone levels increased to 3.1 mIU/mL and 3.6 mIU/mL, respectively, 1 month after the operation and her menstrual cycle recovered spontaneously at 2 months postoperatively. She noticed that the hirsutism had gradually improved 4 months after the surgery.

3. Discussion

Although polycystic ovarian syndrome is the most commonly encountered endocrine disorder that causes hirsutism with hyperandrogenism, an androgen-producing ovarian tumor is also an underlying cause of virilism. Sertoli--Leydig cell tumors are the most common androgen-producing tumors, but they are rare, with a reported incidence of less than 0.5%, and are almost always unilateral [1]. Histologically, the ovarian tumor in this patient was diagnosed as Leydig cell tumor. Although Sertoli–Leydig cell tumors contain both Sertoli cells and Leydig cells, pure Sertoli cell tumors or pure Leydig cell tumors also exist. Sertoli cell tumors are usually estrogenic and also secrete renin. Therefore, these tumors induce hypertension and hypokalemia. By contrast, pure Leydig cell tumors are androgen-secreting [2,3]. Our patient had a pure Leydig cell tumor, which was consistent with her extremely high serum androgen level (11.1 ng/mL) and low serum estradiol level (19 pg/mL). The low serum estradiol level could be explained by suppression of luteinizing hormone and follicle-stimulating hormone due to negative feedback induced by hyperandrogenism; however, it was also partially due to the fact that the tumor was not a Sertoli–Leydig cell tumor but a non-estrogenic Leydig cell tumor. Leydig cell tumors are rarer than Sertoli--Leydig cell tumors among androgen-producing tumors [5] and have some characteristics that are distinct from those of Sertoli–Leydig cell tumors. Patients with Leydig cell tumors are likely to be older than those with Sertoli–Leydig cell tumors (58 years vs. 24 years). Moreover, although most Sertoli–Leydig cell tumors are large enough to be detected by pelvic examination or diagnostic imaging, Leydig cell tumors are small and difficult to detected. Furthermore, most Leydig cell tumors are benign, whereas about 20% of Sertoli–Leydig cell tumors have been reported to be clinically malignant [6,7]. Our patient was a 39-year-old premenopausal woman but satisfied the criteria for a pure Leydig cell tumor.

In this case, we were able to detect the androgen-producing source prior to surgery and performed a laparoscopic right oophorectomy. It is important to be able to localize a hormone-secreting tumor preoperatively, especially in patients who are still of reproductive age. We speculated on the location of the androgen-producing source from measurement of androgen levels by selective venous sampling. If we had not used this technique, we might have had no choice but to perform bilateral oophorectomy. Indeed, we could not distinguish the tumor-containing ovary with the naked eye intraoperatively. Conventional imaging studies such as ultrasonography, computed tomography, and magnetic resonance imaging can usually localize a hormone-producing tumor when it reaches a sufficient size. Furthermore, there have been reports on the usefulness of transvaginal color Doppler ultrasonography [8] and positron emission tomography CT [9]. However, some tumors are too

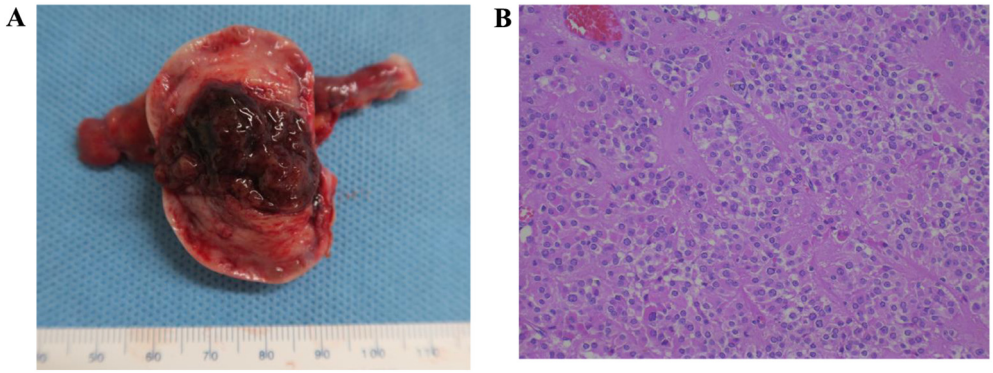

Fig. 1. Macroscopic and microscopic appearance of the right ovarian tumor. (A) Macroscopic appearance of the tumor. On a cross-sectional view, the tumor was a well-delineated, brown solid mass measuring 1.5 × 1.5 × 1.3 cm. The tumor was located in the hilum of the ovary. (B) Microscopic appearance of the right ovarian tumor (see text for a detailed explanation). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

small to detect, so making the differential diagnosis difficult before surgical exploration.

Selective venous sampling is a useful technique for localization of an androgen-producing tumor [10]. In women, androgens are secreted by the ovaries and adrenal glands, and sampling of both organs is necessary. In our case, samples were taken from both ovarian veins to determine the site of the androgen-producing tumor and confirm if the origin of the androgens was an ovary. In addition, samples were taken from the left adrenal vein and upper inferior vena cava to determine whether the origin was an adrenal gland. Cannulation is invasive and technically difficult. In our case, selective venous catheterization was performed by a highly skilled interventional radiologist.

After removal of the androgen-producing ovary, the patient's serum testosterone level returned rapidly to normal (by postoperative day 2) and her menstrual cycle resumed spontaneously 2 months after the operation. Her postoperative progress was similar to that of a 37-year-old woman with a Leydig cell tumor in the right ovary reported by Nishiyama et al. [10]. Our patient noticed gradual improvement of the hirsutism by 4 months after the operation. Much more time is needed for improvement of hirsutism compared with recovery of menstruation.

In summary, we encountered a patient with hyperandrogenism caused by a pure Leydig cell tumor in an ovary. When the hormone-secreting origin cannot be detected on imaging, selective venous sampling should be considered.

Contributors

Aki Oride contributed to drafting the manuscript.

Haruhiko Kanasaki contributed to editing and revision of the manuscript.

Hiroe Okada contributed to acquisition of data.

Satoru Kyo contributed to review of the manuscript.

All authors approved the final article.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Patient Consent

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