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Case Report

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Stromal Luteoma of The Ovary as A Cause of Virilization in A Premenopausal Woman

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Abstract

An ovarian luteoma is a steroid cell tumor of the ovary that has a very low incidence. It usually occurs in postmenopausal women, presenting with symptoms of hyperestrogenism or else hyperandrogenism because it is a hormone-secreting tumor.

We report the case of a 46-year-old female patient referred to the Gynecologic Endocrinology Section for secondary amenorrhea and virilization. Hormone laboratory tests and imaging studies were ordered. Total testosterone levels were suggestive of tumor production. No conclusive evidence of lesions was found, either in the adrenal glands or in the ovaries. Because of the clinical and laboratory suspicion of an androgen-producing tumor of the ovary, bilateral laparoscopic oophorectomy was performed, which revealed a lesion 1.3 cm in size in the left ovary. The lesion was pathologically diagnosed as ovarian stromal luteoma. The patient made good progress after surgery, with remission of hyperandrogenic symptoms.

Keywords: Ovarian Luteoma, Virilization, Hyperandrogenism, Ovarian Tumor

Introduction

Given the complex embryological development of the ovary, tumors of highly varied histological features may occur in this organ, each with specific biologic behavior that will determine different clinical presentations [1, 2].

According to the 1995 WHO classification, ovarian tumors may be histologically divided into:

- Tumors derived from the surface epithelium.
- Tumors derived from the germ cells.
- Tumors arising from the stroma of the ovary and sex cords.

The latter account for approximately 7% of all ovarian tumors and, according to their histological type, they may be divided into: pure stromal tumors, pure sex cord tumors and mixed sex cord-stromal tumors. Pure stromal tumors include steroid cell tumors, which account for 0.1% of all ovarian tumors. These tumors, in turn, are subdivided into three types: stromal luteoma of the ovary (20-25%), Leydig cell tumor (20-25%) and steroid cell tumors not otherwise specified (50-60%) [3-5].

A stromal luteoma is generally a unilateral, well-circumscribed small solid tumor composed of luteinized cells without Reinke crystalloids, located within the ovarian stroma and which may be associated with ovarian hyperthecosis [5]. It occurs in postmenopausal women and symptoms differ depending on the hormones secreted from the tumor. Despite its benignity, it is treated with surgery to resolve symptoms secondary to excessive hormone production.

Case report

A 46-year-old female patient presented to the Gynecologic Endocrinology Section at our hospital in November 2019, referred by her primary physician for hirsutism, alopecia and amenorrhea of

18 months duration.

The patient was a non-smoker with a sedentary lifestyle. She had a history of total thyroidectomy for papillary thyroid carcinoma under treatment with 137 micrograms/ day of levothyroxine.

Since 2006, the patient had been on metformin 1500 mg daily for being diagnosed with metabolic syndrome.

Menarche had occurred at the age of 14 and she had regular menses until July 2018. She had a history of thrombophilia with 8 pregnancies that ended in miscarriage. On physical examination, she had a body weight of 81 kg, a height of 169 cm, a body mass index (BMI) of 28 kg/m2, a waist circumference of 98 cm; blood pressure was 120/70 mmHg, the Ferriman and Gallwey score was 16, with absence of Cushing signs, presence of clitoromegaly and severe temporoparietal alopecia. Figure 1.

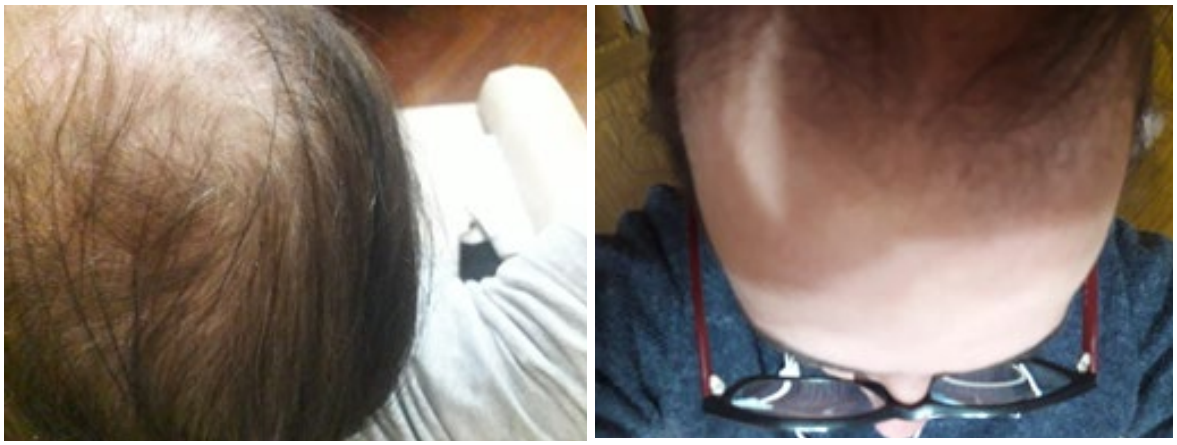

Figure 1: Androgenetic alopecia

At her first visit, the patient provided previous studies:

a) Laboratory tests showing polycythemia and hyperandrogenism at the expense of an almost 4-fold increase in total testosterone levels. See table 1.

Table 1: Baseline laboratory values

		Reference value
Hematocrit	50%	36.1 - 44%
Hemoglobin	16 gm/dL	11.6 – 15 gm/dL
Glucose	80 mg/dL	Less than 100 mg/dL
HbA1c	5.4%	Lower than 5.7%
FSH	7.7 mIU/ml	EFP 4.7 – 21.5 mIU/ml
LH	8 mIU/ml	EFP 2.1 – 10.9 mIU/ml
E2	24 pg/ml	EFP 21 - 251 pg/ml
Prolactin	6.7 ng/ml	EFP 5.18 – 26.53 ng/ml
DHEA-S	1516 ng/ml	1480 - 4070 ng/ml
Δ_4A	1.6 ng/ml	EFP 0.3 – 3.5 ng/ml
17-OHP	0.7 ng/ml	EFP 0.15 – 1.10 ng/ml
SHBG	42 nmol/ml	18 - 144 nmol/l
TT	3.1 ng/ml	Up to 0.8 ng/ml
FT	9.1 pg/ml	0.77 – 9.30 pg/ml
BioT	1.21 ng/ml	0.01 – 0.22 ng/ml

(FSH = Follicle-stimulating hormone, EFP = early follicular phase, LH = luteinizing hormone, E2 = estradiol, DHEA-S = dehydroepiandrosterone sulfate, Δ 4A = Androstenedione, 17-OHP = 17-hydroxyprogesterone, SHBG = sex hormone-binding globulin, TT = total testosterone, FT = free testosterone, BioT = bioavailable testosterone).

b) Transvaginal ultrasound with color Doppler imaging of both ovaries showing: uterus in anteversion and anteflexion 107 x 53 x 86 mm in size with an endometrial thickness of 4 mm, left ovary with a volume of 10 cm3 containing a nonspecific lesion 9 x 7 mm in size with a volume of 12 cm3, right ovary with a volume of 7.7 cm3. Both ovaries contained follicles 4-5 mm in size.

Because of the high hormone levels, repeat laboratory tests and further imaging studies were ordered. Repeat labs revealed TT levels of 3.8 ng/ml (normal range [NR] < 0.8 ng/ml), bioT levels of 1.46 ng/ml (NR 0.01-0.22 ng/ml) and DHEA-S levels of 1773 ng/ml (NR 1480-4070 ng/ml).

A computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast administration showed adrenal glands of normal appearance, no nodular lesions, enlarged uterus of globular shape and no evidence of ovarian lesions.

A magnetic resonance imaging (MRI) scan of the abdomen and pelvis demonstrated enlarged, globular uterus of 105 x 74 x 80 cm in size. The scan showed a posterior, heterogeneous, ill-defined and oval-shaped mass that measures 7 x 6.3 x4.2 cm and bulges the endometrial cavity contour, consistent with focal adenomyosis. No abnormalities were seen in the cervix, vagina, bladder or urethra. Both ovaries had a normal appearance and size, with no lesions. No pelvic lymph node enlargement was noted.

Given the impossibility of performing selective venous catheterization at our institution to identify the source of excessive hormone production due to lack of experience in this technique, a suppression test was performed with a gonadotropin-releasing hormone agonist (GnRHa), leuprolide acetate 3.75 mg. Table 2 shows hormone measurements at baseline and at 15 days after the GnRHa administration.

Table 2: Values obtained with the GnRHa suppression test.

	Baseline values	Post suppression values	Reference values
TT (ng/ml)	3.1	1.8	Up to 0.8
BioT (ng/ml)	1.2	0.6	0.01 - 0.21
Δ4A (ng/ml)	1.6	1.5	0.3 - 3.5
FSH (mIU/ml)	7.7	3.2	4.7 - 21.5
LH (mIU/ml)	8	0.5	2.1 - 10.9
E2 (pg/ml)	24	Less than 10	21 - 251

Based on a diagnosis of severe hyperandrogenism of rapid progression, which is suggestive of tumor etiology, and given the presence of markedly increased TT levels showing suppression after the GnRHa test, normal levels of DHEA-S, Δ4A and 17-OHP, and an absence of adrenal lesions or Cushing signs, the patient underwent bilateral laparoscopic salpingo-oophorectomhy. The pathological examination of the resected material revealed a right ovary of 48 x 30 x 20 mm in size, with presence of white bodies and a follicular cyst. The left ovary was 50 x 40 x 20 mm in size, with white bodies, cystic cavities and a yellowish 13-mm nodule. The Fallopian tubes were unremarkable. The nodule noted in the left ovary was composed of luteinized cells with lipofuscin deposits and a central area with loose fibrous tissue. A diagnosis of stromal luteoma and fibrous adenoma was made. Figure 2.

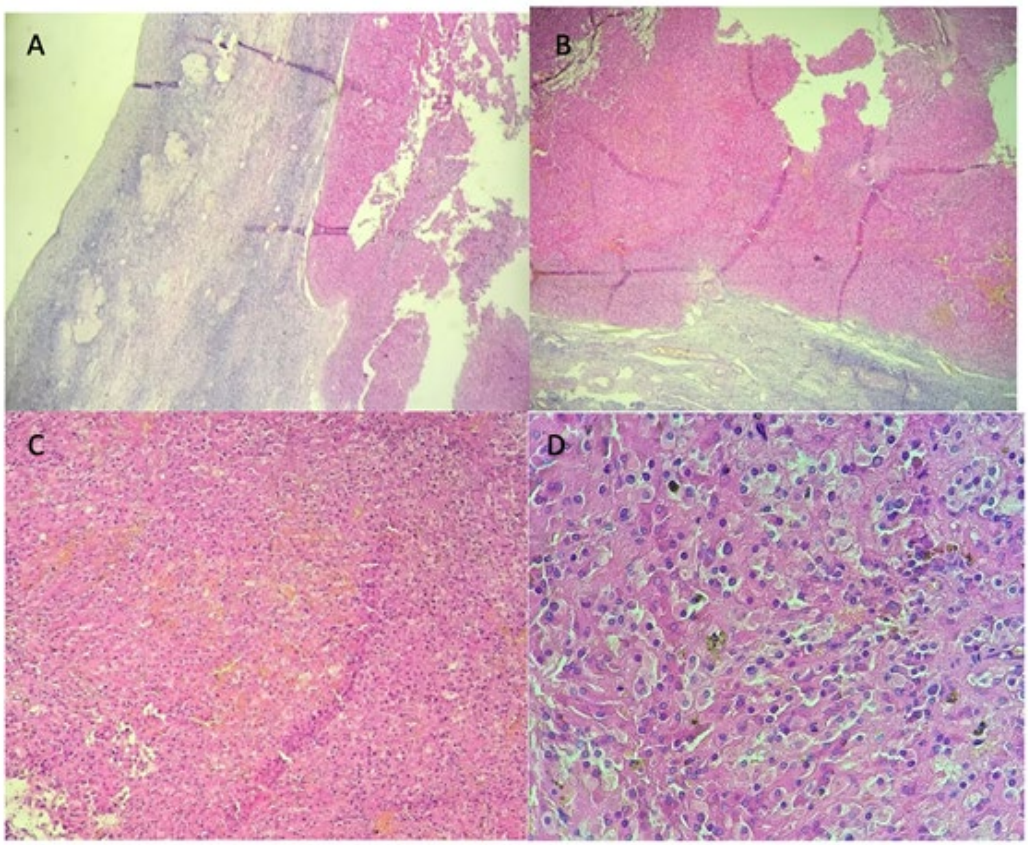

Figure 2A: Ovarian parenchyma on the left, luteoma on the right (ovarian cortex with surface epithelium and stroma with circinate sclerosis), B-D: Well-circumscribed nodule composed of luteinized cells with lipofuscin deposits and a central area with loose fibrous tissue.

The patient's postoperative course was good. Follow-up laboratory tests were performed 10 days after surgery, showing a return to normal levels of androgenic hormones. Table 3.

Table 3: Values obtained 10 days after surgery.

	Baseline	Post GnRHa	Post-surgery
TT (ng/ml)	3.1	1.8	0.1
BioT (ng/ml)	1.2	0.6	0.04
Δ_4A (ng/ml)	1.6	1.5	1.5
FSH (mIU/ml)	7.7	3.2	41.7
LH (mIU/ml)	8	0.5	13.4
E2 (pg/ml)	24	<10	<10

Following surgery, the patient reported mild, tolerable menopausal symptoms that were not treated because of her diagnosis of thrombophilia. The patient reported no changes in sexual desire. The dose of metformin was decreased to 850 mg/day and there was a great improvement in hirsutism. One year after surgery, the patient's alopecia had significantly improved. Figure 3.

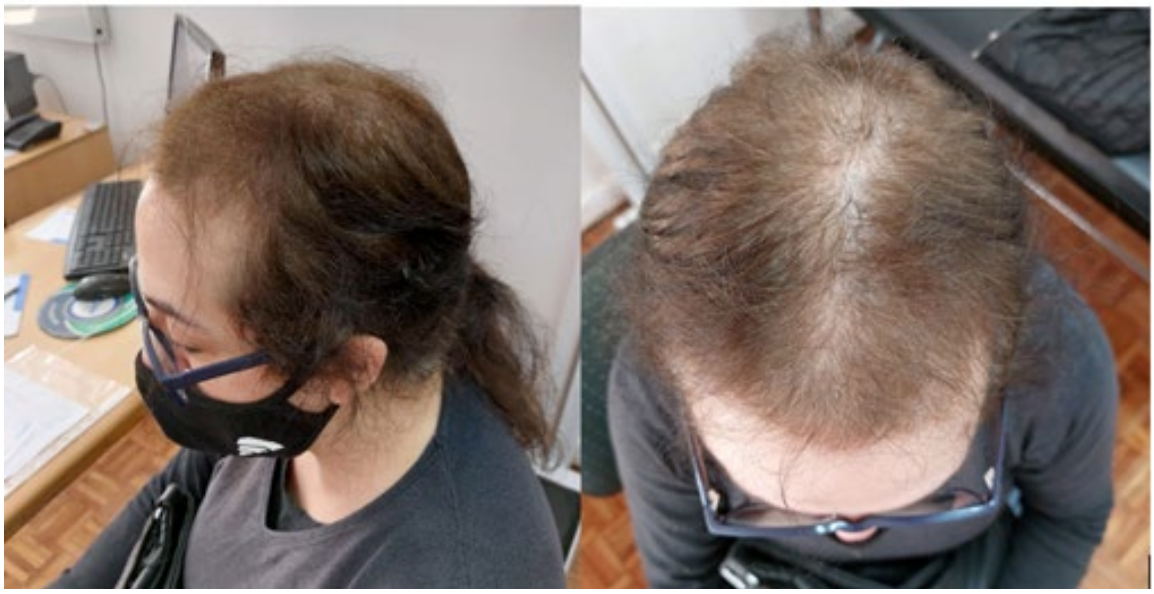

Figure 3: Alopecia recovery one year after surgery.

Discussion

Stromal luteoma is a rare ovarian tumor that occurs mainly in postmenopausal women. Estrogen production with abnormal vaginal bleeding is the most common initial symptom, present in 60% of patients. Twelve percent of patients with stromal luteoma exhibit virilizing signs as a consequence of excessive androgen production. In up to 20% of cases, stromal luteoma may be an unexpected surgical finding [2, 6, 7].

Androgen-producing tumors usually secrete testosterone levels that exceed 2 ng/ml, reaching male ranges. This high testosterone secretion may inhibit LH and FSH levels [8].

The presence of normal levels of DHEA-S, Δ4A and 17-OHP associated with a GnRHa suppression test with a decrease in gonadotropin and testosterone levels allows differentiating an adrenal from an ovarian source of excessive androgen production, indicating the presence of a virilizing ovarian tumor in this patient. This suppression of testosterone production by the GnRHa is due to the incomplete autonomy of androgen-producing ovarian tumors [8-10].

Luteomas are often small-sized tumors, less than 3 cm in diameter; therefore, they are often missed on the various complementary imaging methods. Occasionally, luteomas are only suspected due to the increase in the volume of 1 ovary or localized increased flow on color Doppler transvaginal ultrasound. When noted, they appear as unilateral solid masses. The lipid content produces areas of low attenuation on CT scans, high signal intensity on MRI and intense enhancement on T1-weighted images following the administration of contrast (gadolinium) [4-6, 11].

Microscopically, these tumors consist of polygonal cells with wide eosinophilic granular cytoplasm with a large nucleus, clumpy chromatin and a centrally located prominent nucleolus. Cells are diffusely arranged in nests or cords [5, 12, 13].

Leydig cell tumors should be considered as differential diagnosis. They are benign unilateral tumors that occur in postmenopausal women, presenting with virilizing symptoms and rarely with estrogenic manifestations. Their final diagnosis is established by the presence of Reinke crystals. Sometimes differential diagnosis includes steroid cell tumors not otherwise specified. These tumors are large in size (mean diameter of 8.4 cm) and are characterized for displaying malignant behavior and occurring in young women (mean age 43 years) [6, 14].

Even if stromal luteomas rarely have malignant courses, treatment is surgical excision in order to achieve remission of symptoms caused by excessive hormone production [5].

We are reporting the case of a 46-year-old female patient referred for amenorrhea and clinical virilizing signs (severe hirsutism, androgenetic alopecia and clitoromegaly) of rapid progression. Laboratory tests revealed polycythemia and highly increased serum total testosterone levels. Although the complementary imaging studies showed no ovarian disease, the absence of Cushing signs, the presence of normal levels of DHEA-S, Δ4A and 17-OHP, associated with a decrease in TT levels after the GnRHa test, suggested the presence of a virilizing ovarian tumor. Consequently, the patient underwent bilateral laparoscopic oophorectomy and the pathology examination revealed a stromal luteoma of the left ovary. The patient made good progress with a return to normal of TT levels as early as 10 days after surgery and gradual remission of hyperandrogenic signs (hirsutism and alopecia). Furthermore, there was an improvement of the metabolic disorder, as metformin requirements decreased.

Conclusion

Because of the low incidence of ovarian luteomas and the difficulties in their imaging diagnosis, these tumors represent a diagnostic challenge.

Clinical symptoms resulting from excessive hormone production, in this case hyperandrogenism with elevated TT levels, the presence of normal levels of DHEA-S, Δ4A and 17-OHP, and suppression of hyperandrogenism with the GnRH test are indicative of a virilizing ovarian tumor.

The pathological examination, showing the absence of Reinke crystals, allowed a final diagnosis of stromal luteoma of the ovary.

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