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Case Report

Bilateral Ovarian Thecoma in a Postmenopausal Woman with Rapidly Progressed Severe Hyperandrogenism

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1. Abstract

1.1. Aims: Sex cord-stromal neoplasms of the ovary are an infrequent cause of androgen excess and virilization in women. We report a case of a 60 years old woman with rapidly progressive signs of virilization and indeterminate pelvic masses at computed tomography imaging.

1.2. Methods: The patient underwent a complete hormonal profile a non conclusive transvaginal ultrasonography and a pelvic computed tomography scan.

1.3. Results: Hormonal serum assays revealed markedly increased serum Testosterone and Δ-4 Androstenedione concentrations whereas Dehydroepiandrosterone-sulfate (DHEA-S) levels were found below the reference interval. An ovarian source of androgens was suspected and therefore performed the bilateral oophorectomy. Ovarian histology demostrated a bilateral ovarian thecoma.

1.4. Conclusion: Our report highlights the importance of a careful evaluation of the hormones source in a case of postmenopausal androgen excess in order to ensure the patient a suitable and prompt treatment.

2. Key words

Ovarian thecoma; Virilization; Androgen-secreting ovarian neoplasms; Rare ovarian tumors; Androgens

3. Introduction

Androgen-secreting ovarian tumors are an infrequent cause of androgen excess in women, with the greatest prevalence of one case every 500 women presenting with clinical hyperandrogenism (0,01-0,25%) [1]. Ovarian thecoma is a rare benign tumor of stromal cell origin which generally occurs in peri- and post-menopausal decades as a unilateral, benign, solid lesion. It represents less than 1% of all ovarian neoplasms [2-5] and is classified within the sex cord-stromal ovarian tumor category. The hystology of ovarian thecoma is characterized by clusters of large, rounded or polyhedric cells and sometimes may embody luteinized cells able to produce steroid hormones [6].Typical thecomas are almost always estrogenic; the virilization due to the hyperandrogenemia caused by a luteinized thecoma in postmenopausal women is extremely rare (about 10% of all the cases) [7]. In this case report we present the unusual case of a 60 years-old woman with a rapidly progressed hirsutism and male-pattern baldness whose pathology was post-surgery diagnosed as a bilateral luteinized ovarian thecoma.

4. Case Report

A 60 years-old Italian woman referred to the gynecological endocrinology outpatient clinic of San Paolo University Hospital in Milan presenting an eighteen months history of progressive fronto-temporal alopecia and whole-body hirsutism.

Previously she had always experienced good health. She got married early and at the age of 18 and 23, delivered vaginally two healthy sons. She was an heavy smoker (approximately 20 cigarettes per day) since she was 30; at 41 she underwent a laparotomic hysterectomy with ovaries preservation, for symptomatic multiple uterine myomas; 2 years before she was diagnosed to have hypertension treated with Ramipril and Amlodipine with a good control of blood pressure.

Physical examination showed class 1 obesity (BMI 31.11 kg/m2), severe hirsutism mostly involving face, chin and chest (score 26 of the modified Ferriman and Gallwey test), and severe hair loss, presenting as a diffuse hair thinning with a male pattern baldness area on the crown (Ludwig score III).

The gynecologycal examination showed regular external genitalia and the lack of appreciable pelvic masses. The patient underwent a complete hormonal profile: prolactin and Thyroid Stimulating Hormone (TSH) levels were normal, serum Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), and estradiol concentrations, were within the normal range for age, 24 mIU/mL, 44 mIU/mL and 63 pg/mL respectively. On the contrary, serum testosterone concentration (2,91 ng/mL) and Δ-4 Androstenedione levels (4,63 ng/mL) were markedly increased, while dehydroepiandrosterone- sulfate (33 μg/100mL) was under expressed. Because

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of sex hormone binding globulin (SHBG) concentration of 23,94 nmol/L, a Free Androgen Index of 42,18% was calculated. The investigation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis Function Revealed Adrenocorticotropin (ACTH), basal cortisol levels, 24-hour Urinary Free Cortisol (UFC) and urinary 17-ketosteroids levels in the normal range.

Transvaginal ultrasound examination showed regularly positioned ovaries, bilaterally enlarged in the absence of clear ultrasonographic signs of ovaric cysts or solid masses but showing a diffuse inhomogeneous hypoechoic echotexture and no clear signs of vascularization on color Doppler investigation (color Score 1-2). The ovaries volume was 4,6 cm^3 for the right ovary and 5,5 cm^3 for the left ovary, while the longest diameter was respectively 35 mm and 34 mm. These ultrasonographic features, although not attributable to a specific ovarian disease, conflicted to the patient's age. Ovarian tumor markers serum dosages (CA 125, CA 19.9, CEA, β-hCG and AFP) were within the normal range.

Abdominal and pelvic Computed Tomography (CT) scans suggested the presence of two solid pelvic masses measuring about 3 cm in diameter. The masses were well-demarcated, roundish, well-enhanced and with corrugated margins. No pathologic findings in other abdominal or pelvic organs were identified nor ascites. Iliac-obturator lympho-nodal enlargement in the site of right iliac artery was detected. The Magnetic Resonance Imaging (MRI) screening for possible pituitary lesions was negative.

In the suspicion of an androgen-secreting ovarian tumor, a laparoscopy with bilateral salpingo-oophorectomy was performed. The macroscopic examination showed, for both ovaries, a plurinodular brownish-yellow appearance, with multiple gray-brownish fragments in the context. Extemporaneous histological examination revealed the presence of bilateral solid benign fibro-stromal lesions. The peritoneal fluid cytology for malignant tumor cells resulted negative. The definitive histological examination was compatible with bilateral ovarian fibro-thecoma, with aspects of luteinized thecoma, described as nests of pale luteinized cells within proliferating spindled cells arranged in fascicles with scant cytoplasm.

Immunoistochemical expression analysis revealed a coherent positivity for Inhibin-alpha. The postoperative course was uncomplicated and the patient was discharged on the fourth day after surgery.

Twelve weeks after surgery the seric androgen levels returned into the normal range and the patient reported a gradual improvement of clinical symptoms: serum Testosterone and Androstenedione levels respectively decreased to 0,14 ng/mL and 0,55 ng/mL with DHEA-S levels normalization (150 µg/100mL).

5. Discussion

Virilization due to hyperandrogenemia is an uncommon possibility in postmenopausal women and particularly if hyperandrogenemia is caused by a luteinized ovarian thecoma. Ovarian thecomas are very infrequent ovarian tumors [8].

They occur mostly in peri- and postmenopausal women, with a mean age of 45, rarely malignant, bilateral in 3% of cases [9].

The clinical presentation is relatively non-specific, usually represented by pelvic discomfort or pain. If hormonally active, they usually secrete estrogens that lead to endometrial hyperplasia and clinically presents with menstrual irregularities or postmenopausal bleeding. Androgenic manifestations are rarely reported and are restricted to the tumors characterized by luteinized cells, as is observed in 10% of thecomas, producing androgens and leading to virilization [7, 10].

Androgen secretion of an ovarian tumor before menarche results in heterosexual precocity with premature pubarche, clitoromegaly, virilizing manifestations and accelerated somatic growth. During reproductive age, the typical picture of androgen secretion is oligo-amenorrhea and progressive virilization through hirsutism, alopecia, clitoromegaly and deepening of the voice. Post-menopausal women only occasionally develop signs of virilism, mostly represented by hirsutism and fronto-temporal baldness [11]. Not all patients with elevated serum testosterone levels display androgenetic alopecia. This may be related to individual differences in the sensitivity of hair follicles to the dihydrotestosterone (DHT) activity.

The great part of the published cases of luteinized thecomas in postmenopausal women show different presentation of the disease [3,8,10]. In the present case hirsutism and male pattern hair loss developed in a relatively short period of time.

A full endocrinological laboratory evaluation is mandatory in patients with clinical hyperandrogenism, in order to detect the androgen excess source and to exclude all the possible endocrinopathies hyperandrogenism-related.

It has been suggested that a single serum testosterone measurement above 2ng/mL may indicate the presence of an androgen secreting tumor [12]. Therefore, a serum testosterone level of 2.9 ng/mL, as we found in our patient, was strongly indicative of the necessity to detect rapidly the source of androgen excess.

Despite the 2 years presence of hypertension could be suggestive of an adrenal involvment, adrenal masses or Cushing's disease were excluded by the abdominal ultrasound scan and the biochemical tests. Furthermore, the disagreement between Testosterone and DHEA-S levels and the concordance with those of Androstenedione Δ-4 clearly oriented on the ovarian origin of the hormones.

The investigation of ovarian fibro-thecomas is based, like all ovarian masses, on ultrasound examination. A broad spectrum of sonographic features is reported. At sonography these types of tumors are usually described as hypoechoic adnexal masses manifesting minimal or moderate blood flow on color Doppler examination

with slighty irregular internal echogenicity and stripy shadows and with or without cystic spaces. Larger tumors are often associated with torsion, hemorrhage, calcification, or complicated with other cystic lesions in mixed echogenic masses. Many women have fluid in the pouch of Douglas [13].

In the present case transvaginal ultrasonography was not greatly helpful, displaying two ovaries with only moderately increased volume with uniform hypoechogenic appearance: a paraphysiological significance given the woman's age. No ovarian masses were clearly visualized and also the markers were negative. The rarity of a bilateral secretory tumor made the diagnosis even more difficult. However, the belief that the disease was of ovarian origin has led to more detailed investigations. The first line therapy of a luteinized thecoma is surgery. Ovarian mass resection is indicated for women in reproductive age who need to preserve fertility and similarly it is recommended in postmenopausal women against a potential ovarian malignancy.

Thecomas generally behave benignly, altought features such as mitotic rate, hemorrage and necrosis in the mass context should be regarded with caution for fibrosarcomas. Testosterone levels can be used as a marker of complete excision and for monitoring the subsequent disease course.

6. Conclusion

This report illustrates a case of virilizing ovarian tumor able to elude the first line medical imaging techniques. It emphasizes the potential pitfalls that may occur in the preoperative evaluation of patients with markedly increased androgens production. Hormonal assays can often guide the physicians to the source of androgen secretion and lead to the proper diagnosis and treatment, resulting in the fairly accurate clinical case management.

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