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Case Report

Atypical Endometrial Cancer, Obesity, Diabetes and Hyperandrogenism

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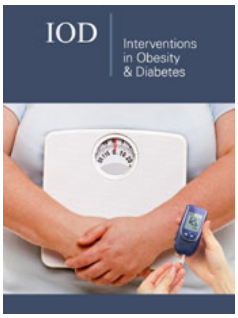

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Abstract

Herein, we report a case of a 50-year-old female patient with advanced endometrioid carcinoma and several associated metabolic and endocrine disturbances. The patient was on hormonal contraception therapy with progestins and was referred because of clinical hyperandrogenism. An ultrasound examination revealed a thickened endometrium and the patient was sent for hysteroscopy, which reported endometrioid adenocarcinoma. In addition to known hypertension, dyslipidemia and type 2 diabetes, metabolic and hormonal laboratory test results showed hyperinsulinemia and hyperandrogenism. Bilateral oophorectomy was performed. The uterus could not be removed due to the advanced stage of disease. The ovaries revealed metastasis from endometrioid carcinoma on a background of bilateral stromal hyperthichotic. In this article, we discuss the role of hyperandrogenism and hyperinsulinemia in the development of this advanced cancer.

Keywords: Endometrial cancer; Hyperinsulinemia; Hyperandrogenism; Obesity; Oligomenorrhea

Introduction

Endometrial cancer is the second most common gynecologic cancer in Argentina, accounting for 6% of all cancers in women [1]. It has a relatively good overall prognosis and is classified as endometrioid and non-endometrioid. The former is the most common subtype and is characterized for being diagnosed at an early stage, being hormone-dependent and having a more favorable clinical course. Risk factors include obesity, hypertension, hyperinsulinemia, chronic exposure to unopposed estrogen (chronic anovulation, polycystic ovary syndrome, late menopause, etc.), and environmental pollutants; conversely, physical exercise and long-term use of Combined Oral Contraceptives (COCs) are associated with a lower risk of endometrial cancer [1,2]. The incidence and mortality rate of this disease is increasing as a result of the growing prevalence of obesity, a known risk factor for the most common type of endometrial cancer [3].

Case Presentation

A fifty-year-old patient was referred to the Menopause and Gynecologic Endocrinology Section of the Gynecology Division at Hospital de Clínicas José de San Martín in April 2023 due to clinical hyperandrogenism with suspected diagnosis of perimenopausal Polycystic Ovary Syndrome (PCOS). The patient was non-smoker, reported no allergies and had a sedentary lifestyle.

Medical history

The patient had myasthenia gravis caused by thymoma at the age of 16. She underwent thymectomy complicated by hemothorax that required blood transfusion. She was then treated with 60mg daily of methyl prednisone for 9 years, which was associated with a weight gain of 40kg, hypertension, amenorrhea and cataract development. She subsequently received azathioprine and pyridostigmine. Currently, she is only on treatment with pyridostigmine. She has a history of blood hypertension since the age of 20, type 2 diabetes diagnosed at the age of 36, cirrhosis secondary to post-transfusion hepatitis C and dyslipidemia at the age of 49. On admission, she was receiving pyridostigmine 60mg/day, enalapril/hydrochlorothiazide 10/25mg/day, amlodipine 5mg/day, metformin 1000mg/day, rosuvastatin 10mg/day and 0.075mg of desogestrel.

Gynecologic history

The patient experienced her menarche at 11 years of age and had irregular menstrual cycles until the age of 16. She started with secondary amenorrhea at this age, concurrent with the intake of high doses of glucocorticoids until the age of 24. After glucocorticoid discontinuation, menstrual cycles resumed, with oligomenorrhea and periods of abnormal uterine bleeding. At the age of 35, due to persistent oligomenorrhea associated with clinical signs of hyperandrogenism (hirsutism, acne), she was diagnosed with PCOS and received COCs consisting of 30 micrograms of ethinylestradiol and 3 milligrams of drospirenone until the age of 49 years, when treatment was switched to Desogestrel (DSG) 75 micrograms until the time of consultation. The patient never got pregnant, on her own accord.

Family history

Mother with hypertension and type 2 diabetes mellitus. Maternal aunt and grandmother with breast cancer.

Physical examination

On physical examination, she had a body weight of 108.600kg, height of 1.58m, Body Mass Index (BMI) of 43.5kg/m^2, blood pressure of 140/70mmHg and heart rate of 76bpm. Her Body Composition (OMRON HBF-514C scale) was body fat 49.6% (Normal Value [NV] for a 40-59-year-old woman: 23-33.9%), muscle mass 32.1% (NV for a 40-59-year-old woman: 24.1-30.1%) and visceral fat 13 (NV≤9). Waist circumference was 132.3cm. Normal thyroid, with no nodules or irregularities detected on palpation. Patient with morbid obesity. Presence of acanthosis nigricans in the neck. Central obesity with presence of pearly white striae over the whole body, a hump on upper back and florid complexion. Normal breast examination. At the time of visit, the patient was on DSG and reported progressive increase in facial and body hair associated with acne. She epilated her facial and body hair every other day and reported thicker and more pigmented hair (Figure 1). The following studies were provided by the patient:

a. Mammography (20-OCT-22): normal breasts, BI-RADS 2.

b. Transvaginal ultrasound (9-MAR-23): regular uterus with heterogeneous, thickened endometrium (22-mm thick). Ovaries of normal sonographic characteristics. Douglas' pouch clear.

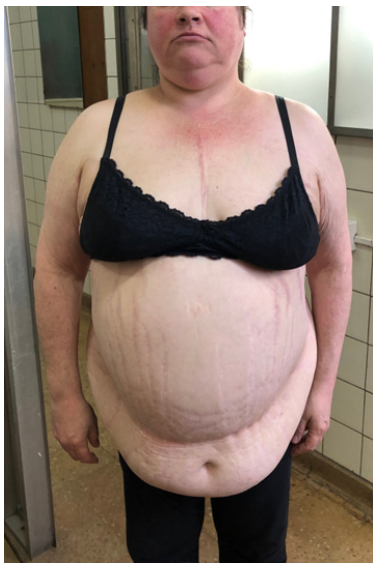

Figure 1: Central obesity with presence of pearly white striae over the whole body.

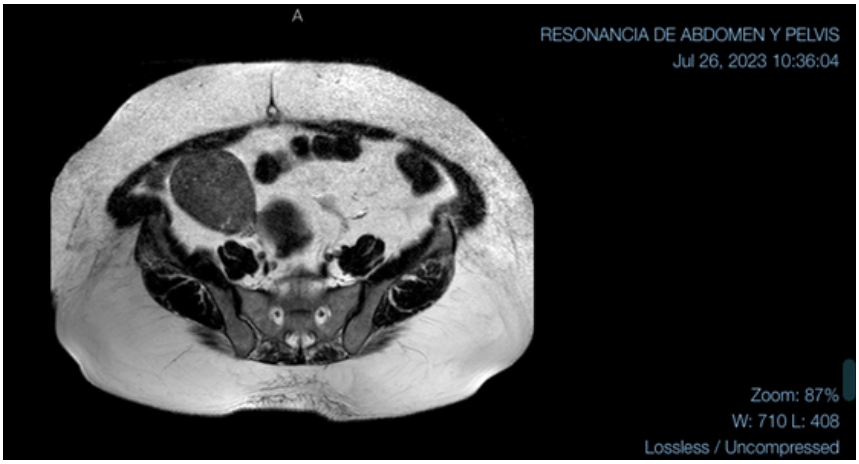

Figure 2: MRI with large mass in the right ovary with projection into the abdominal cavity in the ipsilateral iliac fossa.

The patient was sent for hysteroscopy for endometrial biopsy and serum androgen measurement was ordered. The hysteroscopy was performed on 10-MAY-23. The endometrial biopsy pathology reported "Moderately Differentiated Endometrioid Adenocarcinoma (G2)." The patient was referred to oncologist, where Magnetic Resonance Imaging (MRI) was ordered for staging purposes (26-JUL-23). The MRI showed uterus in anteversion and anteflexion, left ovary with some cystic lesions of homogeneous content and, in the right ovary, an extensive solid mass, 82-mm in diameter, homogeneously enhancing after contrast administration, with projection into the abdominal cavity in the ipsilateral iliac fossa. Even if this lesion could be consistent with adnexal disease, an extensive subserosal myoma could not be ruled out. The scan showed no enlarged endopelvic or inguinal lymph nodes. Further evaluation by transvaginal ultrasound was suggested (Figure 2 & 3).

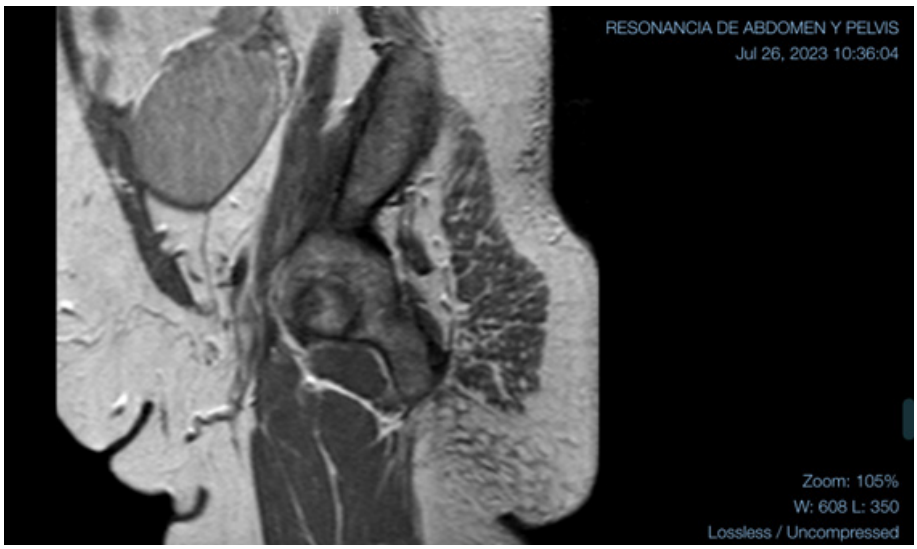

Figure 3: MRI with extensive solid mass, 82-mm in diameter, homogeneously enhancing after contrast administration.

The oncologist ordered tumor marker testing, which was negative, and transvaginal Doppler ultrasound, which was performed on 4-OCT-23. The ultrasound scan showed a 15-mm endometrium. Right adnexal region with cystic lesion with wall thickening in an area that exhibited increased vascularity. The lesion measured 21 x 14mm. The left ovary was not visible. Douglas' pouch clear. In close contact with the fundus of uterus, there was a well-defined, hypoechoic, heterogeneous nodular lesion of solid appearance measuring 104 x 73 x 87mm and with poor peripheral signal on power angio. The patient provided the results of the laboratory tests performed on 9-OCT-23 (Table 1) while on treatment with DSG: total cholesterol 106mg/dL, High-Density Lipoprotein (HDL) cholesterol 71mg/dL, triglycerides (TG) 75mg/dL blood glucose 104mg/dL, insulin 65.6 μ IU/ml, nocturnal salivary cortisol (11 p.m.) 0.17 μ g/dL (NV<0.43 μ g/dL), estradiol (E2) 37.6pg/mL , Estrone (E1) 144pg/mL, Follicle-Stimulating Hormone (FSH) 8.5mIU/ml, Luteinizing Hormone (LH) 5.3mIU/mL, Total Testosterone (TT) 0.73ng/mL, Free Testosterone (FT) 8.04pg/mL, delta-4-androstenedione (D4A) 2.02ng/mL, 17-hydroxyprogesterone (17-OHP) 4.23ng/mL (Figure 4). On 29-NOV-2023, the patient underwent exploratory laparotomy with peritoneal lavage, bilateral adnexectomy, omentectomy and biopsy sampling. The study showed multiple implants <1cm in the parietal peritoneum. Implants were found in the liver, the serosa of the small intestine, colon and mesocolon. Samples were collected for pathology examination. The momentum contained multiple nodular masses. The right ad nexus was enlarged at the expense of an approximately 8-cm cystic mass with smooth surface and fluid content. Bilateral adnexectomy was performed. The intraoperative pathology of the right ad nexus and implants showed infiltration by endometrioid carcinoma. Fixed uterus with infiltrating implants in the vesicouterine junction and left parametrium. Given the impossibility of respectability, a decision was made not to perform hysterectomy.

Table 1: Pre-surgical hormone levels (on DSG) and 48 hours after surgery. Abbreviations: 17-OHP: 17-Hydroxyprogesterone, CLIA: Chemiluminescent Immunoassay, D4A: Delta-4-Androstenedione, DHEAS: Dehydroepiandrosterone Sulfate, E1: Estrone, E2: Estradiol, ECLIA: Electrochemiluminescence Immunoassay, FSH: Follicle-Stimulating Hormone, FT: Free Testosterone, LH: Luteinizing Hormone, NA: Not Applicable, NV: Normal Value, RIA: Radioimmunoassay, TT: Total Testosterone.

Date	LH (ECLIA) mIU/mL	FSH (ECLIA) mIU/mL	E2 (ECLIA) pg/mL	E1 (RIA) NV: 39-132 pg/mL	TT (ECLIA) NV: 0.12-0.48 ng/mL	FT (calculated) NV: <9.3 pg/mL	DHEAS (ECLIA) ng/mL	D4A (ECLIA) NV: 0.49-1.31 ng/mL	17OHP (CLIA) ng/mL
9-Oct	5.3	8.5	37.6	144	0.73	8.04	817	2.02	4.23
1-Dec	9.3	8.9	<26	45	<0.12	NA	239	<0.15	0.16

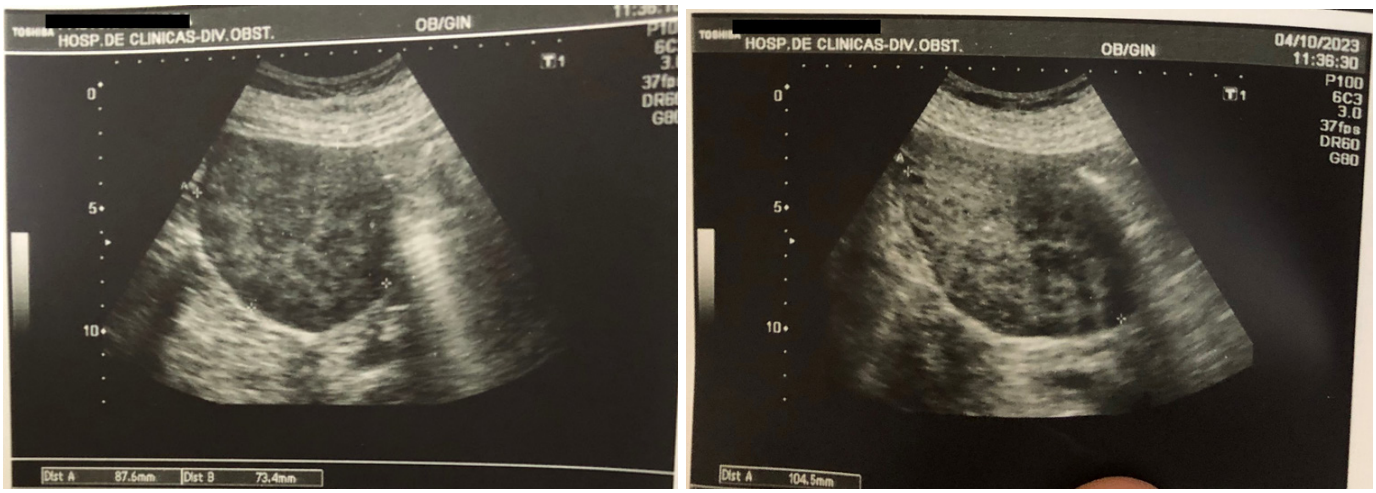

Figure 4: Ultrasound with hypoechoic, heterogeneous nodular lesion of solid appearance measuring 104 x 73 x 87mm and with poor peripheral signal on power angio.

DSG was discontinued on the day of surgery and blood tests were performed 48 hours after surgery (1-DEC-23) (Table 1). The pathology report of the surgical specimen revealed:

i. Right and left adnexa: Bilateral Ovarian Metastasis From Endometrioid Carcinoma (G2) 15 X 1cm and 6 x 3cm in size, respectively.

ii. Bilateral Stromal Hyperthichotic. Tubes with no abnormalities.

iii. Lymph vascular Invasion: Present

iv. Implants and momentum: Infiltration by Carcinoma

v. Peritoneal lavage; cytology: Positive for Neoplastic Cells.

The patient is currently being treated by the gynecologic oncology section with paclitaxel and carboplatin (Figure 5).

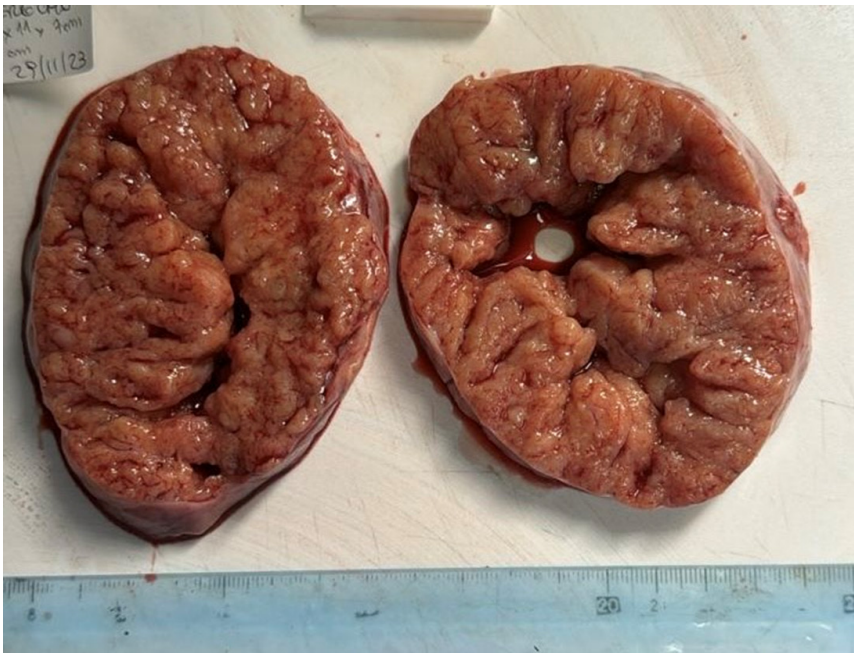

Figure 5: A solid friable golden-brown right ovarian mass (15cm).

Discussion

This case history apparently began with the alteration of the patient's menstrual cycles in adolescence, when she already experienced oligomenorrhea with a normal BMI of 24.8kg/m^2, despite a gynecological age of 5 years. With the development of a thymoma and treatment with high doses of glucocorticoids, her BMI increased to 43.5Kg/m^2 and the patient become amenorrhea. Upon discontinuation of glucocorticoids, oligomenorrhea resumed, which was associated with clinical hyperandrogenism (hirsutism, acne). Therefore, she was diagnosed with PCOS and was prescribed COCs. She received COCs for 14 years and then was switched to progestins alone. The risk factors for hormone-dependent endometrial cancer include the widely known triad of

hypertension, obesity and diabetes, which was already present in this patient at the age of 36 years [2]. The use of COCs is known to have a protective effect against endometrial cancer [4-6]. This is due to the suppressive action of COCs on LH production, resulting in decreased steroidogenic activity with lower production of ovarian androgens, which will be subsequently converted to estrogen. In addition, the estrogenic component of COCs stimulates the production of Sex-Hormone-Binding Globulin (SHBG), with a consequent decrease in free estrogens [7].

However, despite the long-term use of COCs, our patient developed endometrial cancer. Even if no hormone measurements prior to the use of contraceptives are available, the correction of menstrual cycles was considered to be sufficient. In addition, the patient's treatment for diabetes was not associated with any changes in her lifestyle that might lead to weight loss. It is known that obesity increases the risk of endometrial cancer due to multiple mechanisms [8-11]. On the one hand, it has been documented that (mainly visceral) obesity increases insulin resistance with compensatory hyperinsulinemia leading to increased signaling of the insulin-IGF-1 axis [12,13]. On the other hand, obesity is associated with an increased aromatase activity in the uterus, converting androgens to estrogens; in addition, decreased SHBG contributes to an increase in free steroids. It is well-known that obesity is associated with an increase in inflammatory cytokines and a decrease in adiponectin, an increase in oxidative stress and advanced glycation end products, and an abnormal immune response, with all these factors being closely associated with the increased risk of cancers seen in obese individuals [14-16].

Finally, Asaka et al. [17] point out that SIRT1 (Sirtuin-1) may be downregulated in normal endometrial glandular cells of obese women, and that downregulation of SIRT1 may be involved in facilitating endometrial carcinogenesis [17]. Thus, in this case, it is not the protective effect of contraceptives but the risk of long-term hyperinsulinemia what seems to prevail. The lack of hormone measurements performed while the patient was on COCs does not allow us to ensure suppression of her ovarian hyperthichotic. However, it was evident that the use of progestins alone did not inhibit androgen production by the nests of theca cells present in hyperthichotic. Could the aggressive behavior of this cancer be attributed to hyperinsulinemia?

Conclusion

Despite regularization of menstrual cycles with COCs in patients with oligomenorrhea and clinical signs of hyperandrogenism, in those who also have diabetes and obesity we should not overlook the harmful role of hyperinsulinemia. Accordingly, in addition to hormone measurements, metabolic screening should be performed with the aim of identifying patients at increased risk of cancer in order to offer a multidisciplinary approach for better management of these women.

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