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Surgical treatment of post-menopausal ovarian hyperandrogenism improves glucometabolic profile alongside clinical hirsutism

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Abstract

Hyperandrogenism during menopause is often underestimated by clinicians and attributed to the natural aging process. Hyperandrogenism can be associated with some metabolic abnormalities linked together in a vicious circle by insulin resistance. We present the case of an elderly woman affected with type 2 diabetes and obesity who reported the occurrence of clinical hirsutism after physiological menopause at the age of 47 years. At presentation, physical examination and Ferriman-Gallwey score revealed a condition of moderate hirsutism, with markedly increased levels of plasma testosterone and delta-4-androstenedione, obesity (body mass index 31.9), and inadequate glycemic control (glycated hemoglobin 65 mmol/mol). The patient underwent a thorough differential diagnosis by a multidisciplinary team approach, including the various causes of hyperandrogenism during menopause. After choosing surgical option as the appropriate treatment, clinical resolution of hirsutism was observed alongside patient satisfaction and marked improvement of the glucometabolic profile.

Keywords

Hirsutism, post-menopause ovarian hyperandrogenism, surgical treatment

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Introduction

Hyperandrogenism is a heterogeneous clinical syndrome that can affect women of reproductive age as well as elderly ones. The excess circulating androgens results in various phenotypes characterized by dermatologic stigmata (acne, oily skin, seborrhea, skin inflammation, hidradenitis suppurativa), facial or truncal hirsutism, alopecia, virilization, and insulin resistance and related metabolic derangements.[1] After menopause, signs and symptoms of hyperandrogenism[2] are often underestimated by clinicians and attributed to the natural aging process. Hyperandrogenism is also associated with some metabolic abnormalities,[3] linked to the impairment of insulin action and sensitivity.[4,5] In turn, insulin resistance may enhance androgen secretion[6] and generate a vicious circle that increases the risk of developing a metabolic syndrome and, eventually, diabetes mellitus.[7] Because of this substantially increased risk of cardiometabolic diseases attributable to hyperandrogenism—especially in postmenopausal women—it is necessary to investigate the source of excess androgens production, starting with an accurate anamnesis and physical examination.[8,9] Potential endogenous sources of elevated circulating androgens include a wide spectrum of diseases that can affect women of all ages: ovarian malignancies, ovarian hypertecosis (OH), polycystic ovary syndrome (PCOS), obesity-induced hyperandrogenism, other endocrinopathies, and adrenal tumors.[10] OH represents the most

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frequent non-neoplastic cause of hyperandrogenism (9.3%) in post-menopausal women.[9,11,12] This disorder is defined as the finding, in the presence of elevated gonadotropin levels characteristic of menopause, of nests of luteinized theca cells in the ovarian stroma that finally cause overproduction of ovarian androgens.[10] The differential diagnosis between OH and virilizing ovarian tumors may be challenging. In this context, laparoscopic bilateral oophorectomy represents the treatment of choice in postmenopausal women because it offers high likelihood of both confirmatory diagnosis and cure. However, as an alternative to surgery, antiandrogens or long-term gonadotropin-releasing hormone (GnRH) agonists can also be used.[13,14]

Here, we report the case of an elderly woman affected by the metabolic syndrome who developed hirsutism and hyperandrogenism after menopause. We also review the diagnostic-therapeutic pathway and describe how metabolic abnormalities improved after laparoscopic oophorectomy.

Case report

A 66-year-old female was referred to the endocrinology outpatient service of our university hospital to investigate her condition of hirsutism, which had progressively developed after the beginning of menopause and significantly worsened over the past year; written informed consent was obtained from the patient. Her clinical history reported a number of concomitant cardiometabolic disorders, including abdominal obesity, hypertension, atherogenic dyslipidemia, and type 2 diabetes. She was taking metformin, glucagon-like peptide-1 receptor agonist (semaglutide), basal insulin, angiotensin-receptor blocker, calcium-channel blocker, furosemide, omega-3-acid ethyl esters, ezetimibe, and rosuvastatin. She reported no personal history of infertility, menstrual irregularity, or hirsutism during her reproductive age, with three full-term births and one spontaneous miscarriage. During the last pregnancy, she developed gestational diabetes, which had been easily managed through carbohydrates restriction and weight control. Menopause occurred physiologically at the age of 47 years. Physical examination revealed remarkable alopecia and excess terminal hairs (greater than 5 mm in length), mostly affecting the face, chest, and abdomen; clitoromegaly was not detected. No cushingoid features or overt signs of virilization were found. The Ferriman-Gallwey score[15] was 20/36, corresponding to a condition of moderate hirsutism (11). Body mass index was 31.9 kg/m^2, and arterial blood pressure was 120/70 mmHg. Blood tests confirmed biochemical hyperandrogenism, with total testosterone levels of 384.5 ng/dl (reference range for women $<$ 35.76), dehydroepiandrosterone sulfate 136.2 µg/dl (reference range $<$ 133), and delta4-androstenedion 6.09 ng/dl (reference range $<$ 3.3). Blood levels of adrenocorticotropic hormone, cortisol, chromogranin A, and ovarian tumor biomarkers (carcinoembryonic antigen, cancer antigen 125, human epididymis protein 4) were all in the normal range. Glycemic control was sub-optimal, as reflected by glycated hemoglobin levels of 8.1% (65 mmol/mol). According to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, the estimated glomerular filtration rate was 44 ml/min/1.73 m^2.[16] Transvaginal ultrasound revealed both ovaries within normal size and location, lacking follicular activity; color Doppler analysis of the ovarian parenchyma showed no vascularization of the right ovary, whereas a slightly enhanced and localized vascular signal was detected in the left ovary. Because this latter finding was inconsistent with the post-menopausal period, abdominal magnetic resonance imaging (MRI) was then performed in light of the reported clinical presentation. The MRI showed a regular size of the left ovary (mm 20 $\times$ 11), inhomogeneous signal intensity in T2 sequences with a minute central area of signal hyperintensity, and intense postcontrast enhancement. As this last finding appeared not to be a univocal interpretation, the patient was referred for a gynecology consultation. Laparoscopic bilateral salpingo-oophorectomy was proposed for making tissue diagnoses and helping manage the patient's care. A histological diagnosis of luteinized thecoma in the left ovary was eventually confirmed. Hirsutism clinical features progressively improved a few weeks after the surgery. Laboratory tests performed at 3 and 6 months of follow-up showed rapid resolution of biochemical hyperandrogenism and significant improvement of body weight and glucometabolic profile. Anthropometrics and main biochemical/hormonal features at presentation and during post-surgery follow-up are summarized in Table 1.

Discussion

Although both OH and PCOS are the most common causes of androgen excess in premenopausal women, their assessment is to be taken into account even in the differential diagnosis of slowly progressing hirsutism occurring in the post-menopausal period. On the other hand, the development of rapid and true virilizing signs points out the need to quickly assess for malignancy.[10]

The identification of the exact cause of androgen excess, however, may not always be evident in the post-menopausal period. Indeed, estrogen levels are reduced abruptly after menopause, while androgen secretion declines gradually, sometimes leading to hyperandrogenic symptoms. This imbalance between androgens and estrogens is amplified in obese women with insulin resistance.[7,17] The relationships between androgen excess, adipose dysfunction, and insulin resistance are extensively documented,[3,4] and numerous studies have reported the association of serum testosterone with insulin resistance,[17] metabolic syndrome, and type 2 diabetes.[7]

There are several potential mechanisms for the association of androgen excess with insulin resistance, including direct and indirect actions of androgens on insulin target tissues, setting up a vicious cycle whereby hyperinsulinemia

Table 1. Anthropometrics and main biochemical features at presentation and at 3 months and 6 months after surgery.

Features	At presentation	3 months	6 months
Weight (Kg)	87	85	83
Height (m)	1.65	—	—
BMI (kg/m^2)	31.9	31.2	30.5
Systolic blood pressure (mmHg)	120	120	125
Diastolic blood pressure (mmHg)	70	70	70
Hb (g/dl)	10.5	11.1	11.4
Creatinine (mg/dl)	1.28	1.24	1.22
Glucose (mg/dl)	115	92	100
HbA1c (mmol/mol)	65	47	49
Total testosterone (ng/dl)	384.5	19.8	19.9
SHBG (nmol/L)	47.60	44.5	41.4
Delta-4-androstenedione (ng/ml)	6.1	1.5	1.8
DHEA-S (µg/dl)	136.2	107.5	121.3
ACTH (pg/ml)	26.1	—	—
Cortisol (µg/dl)	14.9	—	—
LH (mUI/ml)	42.1	44.2	—
FSH (mUI/ml)	68.5	85.7	—
Total cholesterol (mg/dl)	127	—	142
HDL cholesterol (mg/dl)	35	—	39
LDL cholesterol (mg/dl)	58	—	73
Triglycerides (mg/dl)	119	—	149
AST (U/L)	35	31	35
ALT (U/L)	61	38	40
GGT (U/L)	87	—	—

BMI: body mass index; Hb: hemoglobin; HbA1c: glycated hemoglobin; SHBG: sex hormone-binding globulin; DHEA-S: dehydroepiandrosterone sulfate; ACTH: adrenocorticotropic hormone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; AST: aspartate amino transferase; ALT: alanine amino transferase; GGT: gamma glutamyl transferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

promotes increased production of androgens, which in turn contributes to insulin resistance.[3] Several studies have demonstrated the direct adverse effects of androgens on insulin action in skeletal muscle and human adipose cells, facilitating the development of central obesity.[3,18] There is evidence that biochemical hyperandrogenism per se is a predictor of metabolic inflexibility irrespective of the presence of insulin resistance and excess body fat, contributing to impaired insulin-stimulated glucose oxidation.[19] In turn, this impaired glucose utilization caused by the excess of androgens induces ectopic fat accumulation in the liver and skeletal muscle, contributing to systemic insulin resistance, atherogenic dyslipidemia, and inflammation and fibrosis in the liver.[18] All these phenomena are linked to an increased risk of cardiovascular events. Ovarian thecoma can present itself in the form of luteinizing hormone (LH)-dependent hyperandrogenism, as this case study reveals. Although we did not conduct a GnRH agonist suppression test, the finding is supported by the fact that LH levels were not suppressed despite the severe androgen excess caused by the virilizing neoplasm.[11,20,21] Accordingly, anti-androgenic treatment can partially improve insulin resistance,[16] highlighting the crucial role of androgen excess on the impairment of insulin action. Therapeutic weight loss programs, together with pharmacological approaches to reduce androgens and insulin resistance, are, therefore, a crucial step in the attempt to reduce the likelihood of cardiovascular disease in a patient with metabolic syndrome. Despite this evidence, hyperandrogenism is often underestimated and not considered of primary clinical relevance during the post-menopausal period. Most women with OH, like the one described in the present case report, typically have a long history of slowly progressive hirsutism, accompanied by abdominal obesity and severe insulin resistance that lead to glucometabolic abnormalities, such as type 2 diabetes, and increased cardiovascular risk. Of note, surgical exeresis of the androgen source not only resolved biochemical hyperandrogenism and clinical hirsutism in our patient but also dramatically improved glucose tolerance and insulin resistance within 6 months, reflecting an overall improvement of the cardiometabolic risk profile.

Conclusion

In the end, our case report confirms the importance of proper assessment and differential diagnosis of hyperandrogenism, even when it occurs in post-menopausal women, and especially when glucometabolic abnormalities coexist. This requires a multidisciplinary approach involving endocrinologists, radiologists, and gynecologists with expertise in

metabolic and post-menopausal ovarian diseases, to optimize therapeutic decision-making and provide the patients with a treatment plan aimed at ameliorating both clinical hirsutism and metabolic profile in the long term.

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