BJCR
Brazilian Journal of Case Reports

PCAA
Publicações Científicas de Acesso Aberto

Case Report

Test With Oral Administration of Clomiphene May Add to Differential Diagnosis of Severe Hyperandrogenism in Postmenopausal Women - A Case Report

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Abstract: A 62-year-old female patient, in menopause since the age of 47, presented with severe and virilizing hyperandrogenism condition that had been progressing for 10 years, with plasma testosterone levels above 500 ng/dL. Medical history included Cushing 's disease in remission since hypophysectomy in 2014 and obesity. On imaging tests, there was an adenoma in the left adrenal gland with normal ovaries. Serum DHEA-sulfate concentrations, however, were normal and pelvic ultrasound and magnetic resonance imaging showed no ovarian lesions. Given the etiological doubt of hyperandrogenism, ovarian or adrenal, an additional test was necessary. However, serum gonadotropin concentrations were low, preventing testing with a GnRH analogue. A test was carried out with Clomiphene - a selective estrogen receptor modulator that stimulates the secretion of gonadotropins - at a dose of 50 mg/day orally for 5 days. Serum testosterone concentrations increased from 670 ng/dL, pre-use, to 893 ng/dL post-use, suggesting ovarian origin. The patient underwent bilateral oophorectomy and a Leydig cell tumor was confirmed. Therefore, we suggest that in women with hyperandrogenism of undefined origin, with suppressed concentrations of plasma gonadotropins, a clomiphene administration test be performed. The significant increase in plasma testosterone concentrations is indicative of the ovarian origin of the condition.

Keywords: Clomiphene; Leydig Cell Tumor; Ovarian Neoplasms; Hyperandrogenism; Postmenopause.

Citation: Sartori YRC, Martins EG, Sebastianes FM. Test with oral administration of clomiphene may add to differential diagnosis of severe hyperandrogenism in postmenopausal women- a case report. Brazilian Journal of Case Reports. 2025 Jan-Dec;05(1):bjcr21.

https://doi.org/10.52600/2763-583X.bjcr.2025.5.1.bjcr21

Received: 16 March 2024
Accepted: 12 September 2024
Published: 18 September 2024

1. Introduction

Hyperandrogenic syndromes encompass disorders characterized by an increase in the production and activity of androgens [1]. When affecting women, they manifest a range of clinical features, including acne, hirsutism, menstrual irregularities, infertility, increased libido, androgenetic alopecia, early miscarriage, metabolic syndrome, and signs of virilization (breast parenchymal atrophy, deepening of the voice, muscle hypertrophy and clitoromegaly) [1, 2].

Hyperandrogenic syndromes in adult women can be classified as virilizing and non-virilizing. Non-virilizing syndromes are characterized by relatively unaltered serum testosterone levels, rarely exceeding 200 ng/dl, remaining slightly elevated or within the normal range [1]. They are associated with non-neoplastic functional pathologies, such as non-classical congenital adrenal hyperplasia, obesity-induced hyperandrogenism, polycystic ovary syndrome, and iatrogenic causes (medications and/or supplements) [1, 2]. In virilizing syndromes, there is a markedly elevated serum testosterone level, typically

exceeding 200 ng/dl, accompanied by signs of virilization [1]. They result from neoplastic (adrenal and ovarian tumors) or functional (ovarian hyperthecosis or cortical stromal hyperplasia) etiologies. Androgen-secreting neoplasias are found in only 0.2% of women with hyperandrogenemia and are more frequently found in the ovaries than in the adrenal glands [1,3]. The diagnosis of these rare neoplasias may be challenging, since physical exam and imaging exams may not clearly identify these tumours [4].

To investigate virilizing syndromes, clinical skills, along with appropriate laboratory tests and imaging techniques, and in many cases, postoperative histopathological examination, are necessary to establish the ovarian or adrenal origin [2, 3, 5]. Besides measuring plasma testosterone levels, it is important to assess the sulfated form of dehydroepiandrosterone (DHEAS), as it is predominantly secreted by the adrenal glands [2, 3]. Elevated concentrations, especially exceeding 800 mcg/dl, suggest adrenal pathologies, with values above 6000 ng/ml indicating adrenal neoplasia [2]. Elevated CA-125 serum levels may suggest an ovarian neoplasia [1]. It is noteworthy that, in patients with Leydig cell tumors, the average time between the onset of symptoms and histological diagnosis is about five years [5].

Suppression tests for testosterone secretion can be conducted in severe hyperandrogenism. One commonly used test in postmenopausal women with high plasma gonadotropin concentrations is the administration of leuprolide, a gonadotropin releasing hormone (GnRH) analog, which, by inducing gonadotropin suppression, leads to a reduction in ovarian origin hyperandrogenism [2].

Imaging techniques are also recommended for localizing androgen-secreting tumors with virilization symptoms. Computed tomography (CT) and magnetic resonance imaging (MRI) are useful for adrenal assessment, although the possibility of incidentalomas should be considered [2]. Due to the small size of these tumors, they can be difficult to identify on radiological imaging, as they are isoecogenic on ultrasound and isodense on CT. For ovarian evaluation, transvaginal pelvic ultrasound is the preferred choice, but the accuracy of the examination is examiner dependent. [2, 6]. However, some ovarian tumors may be very small and difficult to be identified. Ultrasonographic exam in these patients may be normal or find only an asymmetry of the organs or a polycystic morphology [2, 4]. In such cases, selective ovarian vein catheterization for local hormonal sampling is an alternative diagnostic method [3]. Among ovarian androgen-secreting neoplasms, those arising from the sex cord-stroma are noteworthy, including Leydig cell tumors, luteoma of the stroma, and steroid cell tumors [1].

Leydig cell tumors are rare neoplasms, accounting for 0.1% of ovarian tumors, composed entirely or predominantly of Leydig cells, without Sertoli cells. They are generally unilateral, solid, with a yellow-brown color, and located in the ovarian hilum, cortex, or medulla. They typically have a diameter ranging from 3 to 5 centimeters. Because they are rare and due to limited research, their natural history, management, and prognosis may be difficult to understand. The standard treatment for these tumors usually involves bilateral oophorectomy because of the potential for bilaterality [3, 5].

Bilateral oophorectomy should also be considered in postmenopausal women with signs of virilization, even in the absence of ovarian or adrenal masses, serving as both a diagnostic and definitive treatment method [3].

Below, we report a case of a postmenopausal patient with a virilizing syndrome, who presented with, an image compatible with adrenal adenoma and a normal ovarian image. She also had low serum gonadotropin concentrations (due to the blockade exerted by the significantly elevated plasma testosterone levels). Considering diagnostic uncertainty, she underwent a test not previously reported in the medical literature, receiving 50-mg of clomiphene citrate orally for 5 days. This increased plasma testosterone levels, suggesting an ovarian source. Consequently, she underwent bilateral oophorectomy, which revealed a Leydig cell tumor.

2. Case Report

A 62-year-old woman, with menopause since the age of 47, presented with severe, progressive, virilizing hyperandrogenism for the past decade. Her plasma testosterone levels had been steadily increasing (295 ng/dL in 2012; 312 ng/dL in 2016; 417 ng/dL in 2019; and 670 ng/dL in 2021). She had a history of Cushing 's disease, which had been in clinical and laboratory remission since hypophysectomy in 2014. However, there was no improvement in hyperandrogenism symptoms or plasma testosterone levels following the resolution of hypercortisolism. On physical examination, the patient had a body mass index (BMI) of 40.5 kg/m2, hirsutism with a modified Ferriman-Gallwey score of 28, muscle hypertrophy, androgenetic alopecia, clitoromegaly, and voice deepening.

The patient had a 20x18 mm nodule in the left adrenal gland on abdominal magnetic resonance imaging, with a marked signal drop in the out-of-phase sequence, consistent with an adenoma. However, there was no elevation in plasma DHEA-sulfate levels. Therefore, there was a possibility that the adrenal adenoma was non-functioning (not hormone-producing). Repeated imaging evaluations of the ovaries, including transvaginal pelvic ultrasound and magnetic resonance imaging, revealed ovaries of normal volume during the postmenopausal period.

When there is doubt about the origin of hyperandrogenism (ovarian or adrenal) in a postmenopausal woman, a suppression test of plasma gonadotropin concentrations (LH and FSH) is typically performed using a GnRH agonist (leuprolide). In this test, when the origin of hyperandrogenism is ovarian, the suppression of gonadotropins reduces plasma testosterone levels. However, in this patient, plasma gonadotropin concentrations were already low because the inhibition of pituitary secretion caused by extremely high plasma sexual steroid levels. This precluded the use of this test in this patient.

To resolve the diagnostic uncertainty regarding the origin of hyperandrogenism (ovarian or adrenal), a test using clomiphene was employed. This medication is a selective modulator of estrogen receptors, antagonizing estrogen's inhibitory effects on pituitary gonadotropin secretion. The increase in LH and FSH concentrations stimulates the secretion of steroid hormones exclusively by the ovaries. For the test, baseline serum testosterone levels were measured, followed by a testosterone measurement one day after 5 days of oral administration of 50 mg/day clomiphene. Because there was an increase in plasma testosterone concentrations (from 670 ng/mL to 893 ng/mL – a 33% increase), the origin of hyperandrogenism was established as ovarian (Table 1).

The patient underwent bilateral oophorectomy, which revealed a 17x15 mm Leydig cell tumor confined to the left ovary. Fifteen days after surgery, plasma testosterone levels became undetectable. Over the following months, the patient showed evident clinical improvement in virilization symptoms.

Table 1. Serum hormone concentrations before and after Clomiphene administration.

	Before Clomiphene Administration	**After 5 Days of Clomiphene Administration**
Total testosterona (ng/dL)	670.79	893.41
Estradiol (pg/ml)	41.1	50.4
FSH (UI/L)	3.1	8
LH (UI/L)	2.5	2.6
SHBG (nmol/L)	24.2	29.2
Free Testosterona (ng/dL)	17.4	22.4

Abbreviations: FSH, follicle-stimulating hormone; FT, free testosterone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin.

3. Discussion

Androgen-secreting ovarian tumors affect about 0.001% to 0.003% of women with hirsutism, but in approximately 75% of cases, there is hirsutism and virilization [7]. Leydig

cell tumor (LCT) is a rare condition, accounting for less than 0.1% of all ovarian tumors. Most cases reported in the literature occur in women in the postmenopausal period, often presenting with high concentrations of testosterone (between 3 and 25 times above the normal limit). However, many of these patients may not exhibit enlarged ovaries on bimanual vaginal examination or abnormalities on pelvic ultrasound. Most of these tumors are unilateral and small, with more than half of the cases associated with virilization symptoms [8, 9]. In the present case, the diagnosis was made 10 years after the onset of symptoms, with testosterone levels nearly 10 times above the normal limit.

Transvaginal ultrasound of the ovaries and computed tomography (CT) or magnetic resonance imaging (MRI) of the adrenals are important diagnostic tools in cases of elevated testosterone levels suggestive of androgen-secreting tumors [8, 10]. Our patient had an image consistent with an adrenal adenoma, which could have been the cause of hyperandrogenism. However, in such cases, there is typically an increase in plasma DHEA-sulfate concentrations, which was not observed in the patient. Nevertheless, normal or slightly elevated DHEA-sulfate concentrations have been described in some patients with testosterone-secreting adrenal neoplasms [11].

Locating ovarian androgen-producing tumors can be challenging due to their small size and the hypoechoic appearance of the uterus in ultrasound and its isodensity in computed tomography [8]. Therefore, the absence of ovarian changes in these imaging exams does not rule out the presence of a tumor, and additional diagnostic tests such as the GnRH analog test are necessary [8, 12]. This test was not feasible for our patient because it requires high plasma gonadotropin concentrations [12]. Another additional examination that could be indicated in such cases is positron emission tomography (PET) with fluorodeoxyglucose (FDG) - abnormal FDG accumulation in one of the ovaries indicates ovarian neoplasia [10]. However, this examination was not performed on the patient because it was not available at the facility where she was being treated. Lastly, bilateral ovarian catheterization can be performed to diagnose ovarian neoplasia, but this procedure is complex and limited to a few specialized centers [10].

A case series study by Fanta et al. [13] showed that the different imaging methods used for diagnosis failed to identify this type of tumor. A gynecological ultrasound, with an appropriate color Doppler configuration, should be ideally performed by a specialist to identify these tumors. Thus, the diagnosis depends on factors such as age (postmenopausal), symptoms, high total plasma testosterone levels, and specialized ultrasound, which is not available in all services [13]. Additionally, Sherf and Martinez confirmed the difficulty in diagnosing these neoplasias solely on biochemical methods or imaging studies, and surgery was needed for diagnosis in many patients [7].

Given this diagnostic challenge, we decided to perform a test aimed at increasing plasma gonadotropin concentrations to assess the response in testosterone secretion. Therefore, clomiphene was administered, leading to a significant increase in plasma testosterone concentrations, consistent with ovarian etiology hyperandrogenism. In postmenopausal women presenting with progressive virilization, androgen-producing ovarian neoplasms should be considered among the diagnostic possibilities [14]. To resolve this uncertainty, given the difficulty in identifying these tumors in imaging tests due to their small size and the fact that pelvic ultrasound depends on the examiner [6], a clomiphene test may be a diagnostic alternative for cases where gonadotropin levels are low.

Although this study shows promising results in using Clomiphene as a diagnostic test for the etiology of virilizing hyperandrogenism in postmenopausal women with suppressed gonadotropins, there are some limitations to this study. This is the only patient described in the literature who underwent this test, which was devised by us. More patients would be needed to confirm the diagnostic utility of this test and its safety in this clinical situation. Considering the rarity of virilizing ovarian neoplasms in postmenopausal women, a case series study with a larger number of patients would be the most feasible approach, comparing the efficacy and safety of this test with other established diagnostic tests.

4. Conclusion

Determining the ovarian or adrenal origin of hyperandrogenism in women with virilizing syndromes can be difficult and may require costly examination or procedures. Oral administration of clomiphene acetate for 5 days is a low-cost test that may prove useful in patients with low plasma gonadotropin concentrations. Larger case studies are necessary to establish the validity of this test in clinical practice.

Funding: Not applicable.

Research Ethics Committee Approval: The following case report was approved by the research ethics committee (#CAAE 69277123.3.0000.5492), and informed consent was obtained from the patient.

Acknowledgments: We would like to thank Andre Faria for his useful help in discussing the best approaches in the treatment of this patient.

Conflicts of Interest: The authors declare no conflicts of interest.

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