CASE REPORT

Cetrorelix suppression test to assess the source of androgen overproduction in postmenopausal hirsutism

Hans de Boer¹, Marian de Man¹, Kim de Bruyn² and Adriaan van Sorge³

Departments of ¹Internal Medicine, ²Clinical Chemistry, ³Clinical Pharmacy, Rijnstate Hospital, Arnhem, The Netherlands

(Correspondence should be addressed to H de Boer who is now at the Department of Internal Medicine, Ziekenhuis Rijnstate, Wagnerlaan 55, 6800 TA Arnhem, The Netherlands; Email: hdeboer@alysis.nl)

Abstract

A 75-year-old woman presenting with recent onset hirsutism and severely elevated serum androgen levels was evaluated to assess the source of excessive androgen production. Commonly recommended hormonal stimulation and suppression tests, and the usually employed imaging techniques were non-diagnostic. In this report, we describe a new suppression test based on the use of the GnRH receptor antagonist, cetrorelix, to determine whether androgen production was LH-dependent. Cetrorelix, administered in a daily dose of 250 µg subcutaneously, suppressed serum LH within 24 h and reduced serum androgen levels to normal within 48–72 h, indicating that androgen overproduction was of ovarian origin. This diagnosis was confirmed by laparoscopic ovariectomy.

Conclusion: The cetrorelix suppression test is a simple procedure that provides valuable information regarding the source of androgen excess in postmenopausal hirsutism.

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Introduction

Recent onset hirsutism in elderly women is highly suggestive of an androgen-secreting ovarian or adrenal tumor (1). Usually, a combination of hormonal suppression and stimulation tests as well as several imaging techniques, such as transvaginal ultrasound and abdominal computed tomography (CT) scans, are needed to localize the source of androgen overproduction. In some cases, additional invasive procedures, such as selective venous sampling or diagnostic laparoscopy, may be necessary (2–4). In this report, we describe a postmenopausal woman with severe hirsutism, where conventional diagnostic procedures failed to provide a definitive diagnosis. A new suppression test, based on the use of a gonadotropin-releasing hormone (GnRH) receptor antagonist, was employed to determine whether androgen overproduction was luteinizing hormone (LH)-dependent and thus likely to be of ovarian origin.

Case report

A 75-year-old woman presented with recent onset hirsutism that had developed in 12 months. For the past 3 months, she had also experienced intermittent vaginal bleeding. Her medical history included breast carcinoma (T1N0M0) at the age of 48, treated successfully with amputation and radiotherapy, postirradiation

hypothyroidism after radioiodine therapy for multinodular goiter at 59, and hypertension for the past 3 years. Menarche was at the age of 14 and was followed by a regular menstrual cycle. Menopause occurred at 55. Current medication comprised simvastatine, lisinopril, temazepam, calcium-carbasalate, metoprolol, and thyroxine. On physical examination, hair growth on the face, back, chest, arms, and legs was significantly increased. The Ferriman–Gallwey score was 19 (normal <8). There was no clitoromegaly nor were there signs suggestive of Cushing's syndrome. Blood samples drawn between 0800 and 1000 h showed a substantial increase in total testosterone (10.3 nmol/l; normal range, 0.2–2.9 nmol/l), androstenedione (30.0 nmol/l; normal range, 1.4–9.4 nmol/l), a modest increase in DHEA (9.8 nmol/l; normal range, 0.3–6.6 nmol/l), and a normal DHEA-sulfate (1.9 µmol/l; normal range, 0.3–5.2 µmol/l). Sex hormone-binding globulin was 39 nmol/l (normal range, 18–114 nmol/l). 17-OH-Progesterone was markedly increased (19.6 nmol/l; normal range, 0.7–4.1 nmol/l). Serum estradiol was mildly elevated (169 pmol/l, normal postmenopausal level, <100 pmol/l), whereas serum gonadotropins were inappropriately low (LH, 14.6 U/l; follicle-stimulating hormone (FSH), 26.1 U/l). Serum cortisol (0.75 µmol/l) and adrenocorticotropin (ACTH; 27 ng/l; normal range, 10–60 ng/l) were normal. A 5-day dexamethasone suppression test (1 mg tid, for 5 days) reduced morning serum cortisol to 0.02 µmol/l, but had no effect on 17-OH-progesterone, testosterone, androstenedione, or

DHEA levels. Stimulation with ACTH, 250 µg intravenously, produced a normal response of 17-OH progesterone (rise from 15.9 to 36.3 nmol/l; normal response, <43 nmol/l). A subsequent abdominal CT scan showed normal adrenals and ovaries. Abdominal and transvaginal ultrasound revealed a relatively large uterus with intrauterine fluid and increased endometrial thickness 10 mm (normally < 5 mm in postmenopausal women). Curettage was performed and the histology showed no signs of malignancies. Scintigraphy with ^{131}I -norcholesterol did not reveal increased uptake in the region of the adrenals or the ovaries. As all conventional tools failed to reveal the source of excessive androgen production and because local experience with venous sampling of the adrenals and ovaries was limited, we designed the cetorelix suppression test. Cetorelix acts as a luteinizing hormone-releasing hormone (LHRH) antagonist, because it competitively blocks the binding of LHRH to pituitary GnRH receptors. The result is a dose-dependent suppression of the release of LH and FSH, which is useful in assisted reproduction techniques to prevent a premature LH surge in women undergoing controlled ovarian stimulation (5). In our patient, 250 µg cetorelix was injected subcutaneously at 0900 h for 4 days. Blood samples were taken at 0830, 1200, and 1600 h during the first day, and at 0830 and 1600 h during the subsequent days. Serum LH decreased rapidly

from 25.5 to 4.6 U/l within 24 h and remained around this level during the next 3 days of treatment (see Fig. 1). 17-OH-Progesterone, DHEA, androstenedione, and testosterone fell to a level within the normal range after 48–72 h. Morning serum cortisol did not change. The results were found to be compatible with an ovarian source of excessive androgen production. Subsequently, the patient underwent laparoscopic bilateral ovariectomy. The left ovary contained a thecoma with a maximal diameter of 2.5 cm. The right ovary was normal. One day after surgery, the total testosterone concentration had normalized (1.6 nmol/l). Four weeks later, serum estradiol had decreased to 57 nmol/l, and this was associated with an increase in LH and FSH to normal postmenopausal levels (34.3 and 75.1 U/l respectively).

Discussion

The present case is illustrative of the diagnostic problems that are commonly encountered during the evaluation of excess androgen in postmenopausal women. None of the usual hormonal tests and imaging techniques produced a reliable diagnosis. The observation that dexamethasone treatment failed to suppress serum androgen levels indicated that androgen production was not ACTH-dependent. When the adrenal CT scan

Figure 1 Hormonal changes in response to 250 µg cetorelix, injected subcutaneously at 0900 h (Δ). The dashed lines represent the upper limit of normal in postmenopausal women. The results shown on the left of the Y-axis represent the samples taken in the basal state between 0800 and 1000 h.

proved to be normal, a tentative diagnosis of ovarian androgen excess was made. However, subsequent examination of the ovaries by transvaginal ultrasound did not reveal a tumor. This is not unusual, because ovarian tumors less than 3 cm in diameter are difficult to detect on CT scan or ultrasound (6). Although ^{131}I -cholesterol scintigraphy may help to show the exact location of androgen production, it failed to do so in the present case (7,8). In experienced hands, venous sampling of the adrenal and ovaries can provide a definitive diagnosis. However, in 50% cases, sampling is inconclusive due to improper catheter placement, and in 5% complications such as infarction or bleeding may occur (1).

The present case illustrates that suppression of LH secretion is useful in localizing the source of androgen excess. Most androgen-producing ovarian tumors contain functional LH receptors and are therefore, responsive to LH stimulation or suppression. Only occasionally, adrenal androgen production may be under the control of gonadotropin, however, this is extremely rare (9). Of course, lack of androgen suppression by cetorelix does not rule out ovarian androgen excess. Loss of LH receptors due to tissue dedifferentiation precludes a response to LH suppression (10). Several case reports have described the use of long-acting GnRH agonists in androgen-producing ovarian tumors (11–13). These agents first produce an increase in LH and testosterone levels, followed by a complete suppression of LH secretion and a subsequent decrease in serum testosterone. The latter may take several weeks to occur (11,13). Therefore, the cetorelix suppression test seems to be preferable as a diagnostic tool because maximal hormone suppression can be observed within several days. Our observations confirm and extend the report of Stephens *et al.* (14), who described a similar case and documented the 24 h hormonal response to cetorelix. Considering gonadal steroid half-lives and the biological variability in LH responsiveness of ovarian tumors, a 24 h cetorelix suppression test is too short to achieve maximal suppression of the relevant androgens. A 3 day test may prove feasible.

In conclusion, this case illustrates that the cetorelix suppression test can provide useful information regarding the source of excessive androgen production in postmenopausal women.

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