Hyperandrogenism in postmenopausal woman: Is surgery reasonable for diagnosis and treatment?

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Abstract

Hyperandrogenism with severe signs of virilism is rare in postmenopausal period. Androgenic drug intake, malign and benign androgen-secreting tumors, gonadotropin depending ovarian stromal disorders have been reported as causes of hyperandrogenism after menopause. We present a 78-year-old woman referred to our gynecology department with hirsutism, male pattern baldness, and deepening voice. Bilateral ovarian enlargement was noted in the gynecologic examination. There was no evidence of adrenal or ovarian tumor with magnetic resonance imaging. The patient’s clinic and laboratory data pointed out an ovarian origin. Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. Both frozen and histopathologic evaluation revealed bilateral ovarian stromal hyperplasia and right ovarian stromal luteoma. The patient was discharged. Three months later, patient’s serum total testosterone level was normal and symptomatic improvement was obtained. Surgery may be reasonable for definitive diagnosis and appropriate treatment of hyperandrogenism of ovarian origin in postmenopausal women who completed childbearing age.

Keywords

Luteoma; Ovarian Stromal Hyperplasia; Postmenopausal Hyperandrogenism

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Hyperandrogenism of ovarian origin is a condition of excessive androgen secretion from the adrenal and/or ovary that manifested with signs of virilism [1]. Differential diagnosis of hyperandrogenism may be difficult. Highly secreted androgens cause clinical manifestations of Hyperandrogenism.

Androgen production that causes hyperandrogenism might be reasonable or benign or malign disorders of the ovary or adrenal glands. It could be seen mostly in the premenopausal period, but this clinical situation is also seen in the postmenopausal period. Increased total-testosterone level and progressive virilism both could be seen with benign/malign ovarian or adrenal gland tumors [2]. Clinicians must keep in mind to separate that tumoral secretion or exogenous administration of androgen.

In postmenopausal period it is hard to diagnose benign tumors which are usually small size. It is also difficult to determine the androgen-secreting tumor originating from whether adrenal or ovarian sources [3].

We present a case of postmenopausal bilateral ovarian stromal hyperplasia and right ovarian stromal luteoma causing hyperandrogenism with severe signs and symptoms of virilism. We used surgery for both diagnosis and treatment. In this report, we sought if surgery is reasonable for both diagnosis and treatment of hyperandrogenism of ovarian origin in the postmenopausal woman.

**Case Report**

A 78-year-old, gravida 4/parity 2 woman presented with hirsutism, male pattern baldness and deepening voice which has progressed within 2-3 years. She has had regular menstrual periods until menopause at the age of 51. Her past medical history revealed well-controlled hypertension and non-insulin dependent diabetes mellitus which has developed 15 and 13 years ago, respectively. General examination was unremarkable except for virilism. Marked hirsutism was on the face and around the umbilicus. Increased hair loss within last year caused alopecia of forehead. Her weight was 78 kg, height was 166 cm (body mass index: 28.31 kg/m²) and obesity was central. Ovaries were found to be palpable in the gynecologic examination and large for her age with transvaginal sonography (right ovary: 55 x 46 x 35 mm and left ovary: 35 x 41 x 27 mm). Uterus and endometrium were atrophic. Clitoral enlargement was not observed. There was no evidence of adrenal or ovarian tumor with magnetic resonance imaging (MRI). In spite of normal serum levels of dehydroepiandrosterone sulfate (DHEAS), androstenedione and 17 hydroxyprogesterone (17 OH P); free testosterone (f-testosterone) (12.7 pg/ml) and total testosterone (t-testosterone) (417 ng/dl) levels were increased (Table 1).

We ruled out Cushing syndrome (CS), androgen insensitivity syndrome (AIS), congenital adrenal hyperplasia (CAH) and an drogenic drug intake by assessing the history, physical examination, and hormone tests. According to increased serum t-testosterone level and large ovaries, hyperandrogenism of ovarian origin was considered. Surgery was offered to the patient as a fast and definitive way for both diagnosis and treatment. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed (Figure 1). Frozen section of the ovaries were benign.

**Table 1. Hormone values before and after surgery**

<table>
<thead>
<tr>
<th>Test</th>
<th>Before surgery</th>
<th>After surgery</th>
<th>Reference range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH (pg/ml)</td>
<td>22.08</td>
<td>7.2 - 63.3</td>
<td></td>
</tr>
<tr>
<td>Cortisol (ug/dl morning)</td>
<td>0.82</td>
<td>6.02 - 18.4</td>
<td></td>
</tr>
<tr>
<td>Cortisol (ug/dl afternoon)</td>
<td>11.49</td>
<td>2.68 - 10.5</td>
<td></td>
</tr>
<tr>
<td>DHEAS (ug/dl)</td>
<td>153.1</td>
<td>12 - 154</td>
<td></td>
</tr>
<tr>
<td>Androstenedione (nmol/l)</td>
<td>4.05</td>
<td>3.5 - 14</td>
<td></td>
</tr>
<tr>
<td>F-testosterone (pg/ml)</td>
<td>12.76</td>
<td>0.49 - 3.1</td>
<td></td>
</tr>
<tr>
<td>t-testosterone (ng/dl)</td>
<td>417.6</td>
<td>2.9 - 40.8</td>
<td></td>
</tr>
<tr>
<td>17 OH P (nmol/l)</td>
<td>2.94</td>
<td>&lt;3</td>
<td></td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>29.4</td>
<td>&lt;5 - 49.9</td>
<td></td>
</tr>
<tr>
<td>FSH (mL/m)</td>
<td>44.2</td>
<td>25.8 - 134.8</td>
<td></td>
</tr>
<tr>
<td>LH (mL/m)</td>
<td>12</td>
<td>7.7 - 59</td>
<td></td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>28.1</td>
<td>26.1 - 110</td>
<td></td>
</tr>
</tbody>
</table>

*postmenopausal referans range

Histopathologic evaluation revealed bilateral ovarian stromal hyperplasia and stromal luteoma on the right side (Figure 2). Both ovaries showed stromal and cortical enlargement with the proliferation of stromal cells. On cross section of the right ovary; gray-white, 12 mm, a nodular tumor was found. The tumor containing homogenous, luteinized nests of polygonal to round cells identified as stromal luteoma. Nucleoli of cells were uniform, and mitotic figures were rare. Reinke bodies were not found.

The patient was discharged on postoperative day three. Her postoperative period was uneventful. Three months later, normal serum t-testosterone level (34.76 ng/dl) and symptomatic improvement were obtained (Table 1).
Postmenopausal hyperandrogenism

Discussion

Hyperandrogenism is a clinical condition of excessive androgen secretion. Benign and malignant disorders of ovaries and adrenals, which are the organs responsible for androgen production, cause hyperandrogenism not only in the premenopausal period, but also postmenopausally [1]. Hormone tests often provide rough definition between ovarian and adrenal origin. CS and CAH were ruled out with normal serum cortisol and 17 OH P levels in our patient. Androgen secreting adrenal tumors are the other important causes of concern. Rapid progressing virilism in various degrees and very high t-testosterone and DHEAS levels were reported with virilizing adrenal tumors [2]. Despite lower incidence of these tumors, malignity risk is higher than virilizing ovarian tumors. Fortunately, they have certain radiologic features, and they are usually large enough to detect with imaging [3,4].

In the patient we presented, hyperandrogenism of ovarian origin was prediagnosed ruling out the adrenal causes and enlarged ovaries with increased t-testosterone level. Reviewing the literature, physiopathology of hyperandrogenism of ovarian origin in postmenopausal woman mostly has been found to be associated with ovarian response to the high levels of gonadotropins. Gonadotropin effect on ovarian stroma can cause hyperplasia of stromal cells leading to excessive androgen production and severe virilism. If the cell hyperplasia dominates, hyperthecosis is referred histopathologically. Stromal hyperplasia or hyperthecosis effects ovaries diffusely, and they can be within each other [5,6]. Furthermore; some benign tumors such as stromal luteoma may be considered as a morphologic variant of the same pathology [7]. Stromal luteoma is defined as a subtype of steroid cell tumor amongst sex-cord stromal tumors. Steroid cell tumors constitute 0.1 % of primary ovarian tumors, and stromal luteomas constitute 20-25 % of steroid cell tumors. Stromal luteomas are usually estrogen secreting, unilateral, benign tumors [8]. Coexistence with endometrial hyperplasia and atrophic endometrium. Although all androgen secreting ovarian tumors have a sex-cord stromal origin, androgen secreting serous cystadenomas and neuroendocrine tumor metastases have also reported in the literature [11,12]. It has been speculated that These tumors stimulate the surrounding stroma and lead hyperplasia via paracrine mechanisms. As it is easier to diagnose malign tumors with imaging or signs of cancer, diagnosis of benign tumors which are usually in small size may be difficult.

PCOS is another benign disorder manifested with bilateral large ovaries and hyperandrogenism. It can rarely be recognized in postmenopausal women who are usually obese or had PCOS premenopauly. Virilism is supposed to be mild and slow progressing in these patients [13]. Differential diagnosis for tumoral and non-tumoral causes of hyperandrogenism of ovarian origin may be difficult. We suspected ovarian stromal hyperplasia, androgen secreting ovarian tumor, and PCOS in this case. Also, a small adrenal tumor might be suspected. Detailed anamnesis, general and gynecologic examinations give precious information for diagnosis. “Adrenal / ovarian venous catheterization and sampling” is a method proposed for differentiation of ovarian and adrenal origin [14]. Because the catheterization of all four adrenal and ovarian veins may be troublesome and needs expertise, it has been used in clinical practice barely. Dexamethasone suppression test is another diagnostic method based on unresponsiveness of adrenal or ovarian tumors to dexamethasone administration while testosterone reduction occurs in nontumorous cases. However; unresponsiveness has been reported with some non-tumoral disorders [15]. Using gonadotropin-releasing hormone agonist (GnRH-a) against gonadotropin stimulus leading to androgen secretion as both diagnostic and therapeutic option has also been reported [16]. Such management that excludes definitive diagnosis is to be appropriate for patients who have high surgical risks.

In conclusion; current diagnostic tools and methods may not be sufficient for differential diagnosis. Although, virilizing malignant tumors are usually detected with imaging and signs of cancer; only pathologic evaluation discloses the diagnosis of benign tumors, which are mostly in small size, and non-tumoral benign pathologic conditions of ovarian stroma. Therefore, surgery is reasonable for definitive diagnosis and treatment in a postmenopausal woman who completed childbearing age.

Consent

The authors declare that written informed consent was obtained from the patient for publication of this case report with accompanying images.

Scientific Responsibility Statement

The authors declare that they are responsible for the article’s scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and...
its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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