CLINICAL STUDY

Use of a long-acting gonadotrophin-releasing hormone analogue in a postmenopausal woman with hyperandrogenism due to a hilus cell tumour

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Abstract

Objective: The aim of this study was to prove the utility of GnRH analogues for the suppression of androgen secretion in a postmenopausal woman with a suspected virilizing ovarian tumour.

Design and Methods: We present a case of a 72-year-old woman with virilization of recent onset. Hormonal studies revealed a fourfold increase in serum testosterone levels, normal dehydroepiandrosterone sulphate concentrations and high levels of serum 17-hydroxyprogesterone levels. Computed axial tomography scan of the ovaries was normal and the adrenal glands showed a discrete enlargement. The long-acting GnRH analogue, triptorelin, was injected initially (3.75 mg i.m.) and serum hormone levels were measured weekly throughout one month.

Results: GnRH produced a decrease in serum testosterone levels to normal values, in parallel with the suppression of serum LH and FSH concentrations. The patient was treated for three months with triptorelin and she experienced an amelioration of the hyperandrogenic symptoms. In order to achieve a diagnosis, the patient was submitted to a laparotomy that revealed a small hilus cell tumour in the left ovary.

Conclusion: GnRH analogues may offer a good therapeutic option in some states of gonadotrophin-dependent hyperandrogenism of ovarian origin.

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Introduction

It has been reported that the secretion of androgens by some ovarian tumours can be inhibited by gonadotrophin-releasing hormone (GnRH) agonists. Different types of testosterone-secreting ovarian tumours showing this kind of hormonal regulation, i.e. Leydig cell tumour, granulosa cell tumour, Sertoli–Leydig cell tumour, hilus cell tumour and stromal luteoma (1–5) have been described. The suppressive effect of GnRH analogues on the secretion of testosterone by the ovarian tumour cells seems to be related to an inhibition of endogenous gonadotrophin secretion.

We report the case of a postmenopausal woman with virilization of recent onset whose high serum androgen levels were normalized after the administration of the long-acting GnRH analogue, triptorelin. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) serum levels were both in the low range of postmenopausal values, and were suppressed by the GnRH agonist. Her symptoms ameliorated following triptorelin administration for three months. A bilateral oophorectomy was performed and a benign hilus cell tumour was found in the left ovary. The patient also presented a non-classic deficiency of 21-hydroxylase.

Case report

A 72-year-old postmenopausal woman, gravida 15, para 7, was referred to our outpatient clinic for evaluation of hirsutism. Her past medical history was remarkable for hypertension diagnosed three years ago that was well controlled with a Ca2⁺ antagonist. Menarche had occurred at the age of 13 years with regular monthly cycles until the cessation of menses at the age of 52 years. The patient complained of a three- to four-year history of progressive hirsutism affecting the body, arms and legs, but predominantly facial, requiring regular shaving. She had noted a
Table 1 Hormone values in the basal situation, after the i.m. administration of 3.75 mg GnRH analogue, triptorelin, and after the removal of the tumour.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Basal</th>
<th>1 week</th>
<th>2 weeks</th>
<th>3 weeks</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>After surgery</th>
<th>Reference range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEAS (nmol/l)</td>
<td>2.6</td>
<td>2.6</td>
<td>2.5</td>
<td>1.8</td>
<td>2.0</td>
<td>3.1</td>
<td>2.0</td>
<td>0.2–2.6</td>
</tr>
<tr>
<td>17-Hydroxyprogesterone (nmol/l)</td>
<td>4.2</td>
<td>4.8</td>
<td>3.9</td>
<td>2.1</td>
<td>2.7</td>
<td>3.6</td>
<td>3.9</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Oestradiol (pmol/l)</td>
<td>311</td>
<td>316</td>
<td>248</td>
<td>244</td>
<td>178</td>
<td>167</td>
<td>248</td>
<td>&lt;93</td>
</tr>
<tr>
<td>Total testosterone (nmol/l)</td>
<td>11.6</td>
<td>15.1</td>
<td>2.7</td>
<td>1.3</td>
<td>1.5</td>
<td>11.6</td>
<td>1.5</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td>Free testosterone (pmol/l)</td>
<td>64.4</td>
<td>39.9</td>
<td>7</td>
<td>3.5</td>
<td>3.9</td>
<td>51.8</td>
<td>14.7</td>
<td>7–17.5</td>
</tr>
<tr>
<td>Androstenedione (nmol/l)</td>
<td>11.6</td>
<td>11.2</td>
<td>5.6</td>
<td>3.5</td>
<td>4.2</td>
<td>8.9</td>
<td>3.5–14</td>
<td></td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>24.4</td>
<td>4.4</td>
<td>1.7</td>
<td>1.3</td>
<td>1.3</td>
<td>23.9</td>
<td>29.1</td>
<td>25–145</td>
</tr>
<tr>
<td>LH (U/L)</td>
<td>12.2</td>
<td>7.8</td>
<td>3.2</td>
<td>1.2</td>
<td>0.4</td>
<td>19.4</td>
<td>25.4</td>
<td>17–71</td>
</tr>
</tbody>
</table>

* Reference values are for postmenopausal women.

diffuse hair loss, acne, and weight increase. She noted neither voice deepening nor a change in libido. Medical history did not reveal any medication in the past five years that might have contributed to the virilization.

The initial physical examination revealed signs of virilization such as beard, masculine alopecia and a male distribution of pubic hair. The clitoris was enlarged and no pelvic mass was palpable; her weight was 88.3 kg, height 153 cm, and body mass index 35.8 kg/m². Her obesity was central without striae and no goiter was palpable. The gynaecological examination disclosed a normal uterus.

Laboratory data on examination, shown in Table 1, revealed high serum levels of total and free testosterone, oestradiol and 17-hydroxyprogesterone; androstenedione and dehydroepiandrosterone sulphate (DHEAS) were in the normal range. LH was in the premenopausal follicular phase and FSH was in the low range for a menopausal woman. Cushing’s syndrome was ruled out by an overnight dexamethasone suppression test (1 mg); the basal serum cortisol level was 400 nmol/l and this decreased to 44.2 nmol/l at 08.00 h on the following day. Basal serum 17-hydroxyprogesterone level was 4.2 nmol/l and increased to 47.7 nmol/l after the intravenous administration of synthetic adrenocorticotrophin (ACTH) (250 μg cosyntropin). Transvaginal ultrasonography of the ovaries revealed high serum levels of total and free testosterone, DHEAS, 17-hydroxyprogesterone and androstenedione rose to basal values two months after triptorelin administration.

The gonadotrophin dependence of the hyperandrogenism in the patient suggested an ovarian disorder not disclosed by routine imaging techniques. The patient was proposed to undergo a surgical ovarian examination, but she was reluctant and was treated with an i.m. injection of triptorelin (3.75 mg) every 28 days for three consecutive months. During this period, she experienced an amelioration of hirsutism, acne, seborrea and loss of hair. Finally, she accepted the surgical examination, and a laparotomy and oophorectomy were performed.

Pathological findings: the bilateral oophorectomy specimens consisted of the right ovary (1.7 × 1.3 × 0.8 cm) and the left ovary (2.7 × 1.4 × 1.3 cm), both of them with unremarkable outer surface appearance. On cross-section, the left ovary showed a 0.9 cm round tumour, tan in colour, located in the centre of the specimen or hilus area.

Microscopic findings: on histological examination, the Leydig cell tumour found in the hilus of the left ovary showed a solid growth, well circumscribed but non-encapsulated, of homogenous polygonal to rounded cells and a rich capillary network. The cells contained eosinophilic, slightly granular cytoplasm, occasionally vacuolated, and were disposed in a sheet arrangement. The tumour cells contained various amounts of periodic acid-schiff-positive ceroid substance. Reinke’s crystalloids were not found. No mitotic figures were detected. Both ovaries showed slight signs of stromal cortical hyperplasia. The tumour cells reacted intensely to vimentin, CD99 and inhibin (M. GUIU, Barcelona, Spain). Immunostaining for cytokeratin (AE1/AE3), epithelial membrane antigen,
Hilus cell tumours represent 20% of steroidogenic cell tumours of the ovaries, which in turn constitute 0.1% of all ovarian tumours. They arise from clusters of large steroidogenic cells, called hilus cells, normally found along the length of the ovaries of adult women (6–8). All aspects of their structure and function are identical to those of differentiated testicular Leydig cells. The hilus and Leydig cells cannot be distinguished by morphological criteria. Both contain a unique hexagonal array of crystals termed Reinke crystalloids that are considered to be pathognomonic, but are usually found in less than 50% of cases (6, 9).

The reported inhibitory effect of GnRH analogues on testosterone secretion by ovarian tumours seems to be mediated by suppression of endogenous gonadotrophins. However, a direct effect of the analogue on tumour cells could also play a role in this suppressive effect. A suppression of testosterone secretion by isolated arhenoblastoma cells cultured in the presence of GnRH analogues (15), and an increase in testosterone secretion by isolated Leydig tumoral cells cultured in the presence of GnRH antagonists (5) has previously been described. The direct effect of GnRH agonists and antagonists on steroidogenesis produced by tumoral cells seems to be related to the presence of GnRH receptors in the cells (5).

The question of gonadotrophin regulation by testosterone in women remains unclear. In our patient, high serum testosterone levels were associated with low serum LH levels, but as serum oestradiol levels were also high, possibly due to testosterone conversion, the
independent role of each hormone on the regulation of gonadotrophins cannot be defined.

In our patient, triptorelin produced a marked inhibition of testosterone secretion, and most of the clinical symptoms reverted during the three-months treatment trial. However, due to the lack of a diagnosis, we insisted on performing a laparoscopic examination. As in the other reports on gonadotrophic-dependent virilizing ovarian tumours, this patient also had a benign tumour.

To our knowledge, there is no experience with the long-term use of GnRH analogues in the treatment of hyperandrogenic ovarian tumours. However, a symptomatic and biochemical improvement has been described in an elderly woman treated for one year with a long-acting analogue of GnRH, who had a hyperandrogenism probably due to an ovarian origin, as suggested by the hormone profile (16). In order to use it for diagnosis and for therapy, it is important to assess whether other states of hyperandrogenism due to ovarian malignant tumours and adrenal tumours are also inhibited by GnRH administration. Short-acting analogues would be useful for diagnostic purposes and longer-acting agents would be useful for treatment.

In conclusion, GnRH analogues may be of clinical benefit for diagnosis and for treatment in some benign testosterone-secreting tumours of the ovaries.

References


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