Causes of virilization in postmenopausal women: case reports

Belgian Menopause Society
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Géraldine Brichant, Axelle Pintiaux
Case # 1
History

• Mrs D: 63 year old woman
• 10 years of
  • temporal and frontal balding
  • without hirsutism
• Unknown etiology
• Vitamin treatment in a dermatologic clinic
• Medical history
  • Menopause at 48 y
  • P2G3, 1 miscarriage
  • Long standing hypertension, hypercholesterolemia, glucose intolerance
Examination

• Good general health
• BMI 24.84 kg/m², BP: 130/70
• Androgenic alopecia
• Increased muscle mass
• No virilization of external genitalia
• No hirsutism, no acne
• No stretch marks, no moon face, no buffalo hump, no acanthosis nigricans
Laboratory tests

- Total Testosterone : 6.1ng/ml (0.02-0.4)
- Glucose level : 113 mg/dl
- DHEA-S : 104.7 µg/dl (29-182)
- LH : 6 mUI/ml
- FSH : 7.6 mUI/ml
- E2 : 19.6 pg/ml
- Cortisol : 427.4 nmol/L (101-535)
Investigations

• Pelvic ultrasonography:
  • Uterus: anteverted: 34/24 mm,
  • Right ovary: 25 mm heterogenous, with some hypoechogenic islets,
  • Left ovary: 15 mm homogenous
  • No ascites
• Pelvic MRI: same description
• Adrenal MRI: normal
Conclusion

• Hypothesis :
  • Benign Ovarian Tumor

• Final diagnosis after oophorectomy
Case # 2
History

- Mrs R: 53 year old woman
- Hirsutism before menarche, increasing now: body shaving every 2 days and facial hair removal every day
- Medical history
  - Menarche at 14
  - Menopause at 52
  - POGO
  - No diagnosis for infertility (treatment by clomiphene and gonadotropins) despite intensive investigation
- Family history: none
Examination

• Good general health
• BMI 23 kg/m², BP: 130/80
• Hirsutism
  • Ferriman Gallway score : 19
• No stretch marks, no moon face, no buffalo hump, no acanthosis nigricans
• No virilization of external genitalia
• No alopecia, no acne
Biology

- Biology prior to menopause - cycle 3rd day:
  - Total Testosterone: 1.10 ng/ml (0.02-0.4)
  - Delta 4 A: > 10 ng/ml (0.3-3.3)
  - DHEA-S: 3971 ng/ml (370-2700)
  - FSH: 7.8 U/L
  - E2: 51 ng/L
  - P: 4.3 µg/L
Investigations

- Progesterone during oral contraception (COC): 7.2 and 3 µg/L
- Hypothesis?
  - 21OH déficiency

- ACTH test: cortisol 26.6 to 26.1 µg/dl and 17OHP: 64 to 105 ng/ml (0.1-5.2)
Case #3

History

- 73 year old woman
- 3-4 years of
  - Temporal and frontal balding
  - Progressive hair growth on chest, back and abdomen
  - No weight loss or sweating
  - Long standing hypertension
- Family history: none
- Medical history:
  - Menarche 16, irregular cycles
  - 3 children
  - Menopause at 40
Physical examination

- Good general health
- Obesity (BMI 31.5 kg/m²), BP: 160/85
- Ferriman-Gallwey score 24/36
- No virilization of external genitalia
- Androgenic alopecia
- 2/6 systolic murmur
- No mass palpable but hernia
Investigations

• Hormonal evaluation
  • Serum total testosterone: 6.86 nmol/l (normal <1.22)
  • Dehydroepiandrosterone sulfate (DHEA-S), androstendione, 17-OH-progesterone and 24 h-urine collection for free cortisol: normal.
  • Transvaginal ultrasonography: enlarged ovaries for age
  • Abdomino-pelvic CT-scan: no tumours of the adrenal glands or ovaries

→ Bilateral ovariectomy
Histopathological examination

- large ovaries
- stromal hyperthecosis with an increase in lutein cells
Evolution

• Postoperative testosterone-level: 0.74 nmol/l
• Hirsutism (Ferriman-Gallwey score 13/36) and androgenic alopecia improved on follow-up.
Ovarian Hyperthecosis

- Luteinized thecal cells in the ovarian stroma
  - Androgen secretion $\rightarrow$ virilisation
- Functional disorder, role of gonadotrophin stimulation
- Usually uneventful menstrual and reproductive history
- Clinical features:
  - Obesity
  - Androgenic alopecia
  - Severe hirsutism
  - Male habitus, clitoromegaly, deepening of the voice
  - Metabolic syndrome
- Several years vs rapid in case of tumors
Ovarian Hyperthecosis

• Biochemical findings
  • Elevated serum free testosterone
  • Normal DHEA-S
  • Non suppressed gonadotropins

• Ultrasonography
  • Average ovarian volume > 6 cm\(^3\) (menopausal volume: 2,5-3,7 cm\(^3\))

• Treatment:
  • bilateral ovariectomy
  • long acting GnRH agonist
Case #4

- International Journal of Dermatology 2009, 48, 993-995
History

• 65-year-old woman
• 3-month history of
  • Face and neck erythema
  • Acne-like eruptions on the cheeks
  • Growth of facial hair on the chin
  • No PMB
  • Deepening of the voice
• Medical history
  • Hypertension
  • Osteoarthritis, lumbago
  • Right-side ovarian cyst removed 20 years previously
  • Insomnia since menopause (50 years old)
• Treatment
  • Antihypertension medication
  • Unknown medicine for insomnia (local clinic)
Physical examination

- BMI: 20.5 (+ 6–7 kg over 5 years)
- Physical examination
  - Chest and abdomen: no abnormalities
  - No palpable masses
  - No spider angioma, caput medusa, buffalo hump
  - No galactorrhea
  - No acanthosis nigricans
Investigations

• Laboratory findings
  • Routine blood counts and biochemistry
    • Estrogen levels at 23.6 pg/mL (0–14 pg/mL)
    • Testosterone at 248.4 ng/dL (6–86 ng/dL)
    • Aldosterone < 2.5 ng/dL (normal, 4–31 ng/dL)
    • Cortisol 3.9 ng/dL (normal, 5–25 ng/dL)
    • CA125, CA153, and (AFP) unremarkable.
    • FSH, LH, TSH, prolactin and GH within normal limits
• Adrenal gland MRI: no abnormality
• Pelvic ultrasonography: no gross ovarian lesions
Treatment

- Unknown medication:
  - Disemone (testosterone enanthate 90.2 mg + estradiol valerate 4 mg)
  - Received IM monthly for 5 years, starting when she was 60 years of age.
- Stopping the latter → Testosterone declined

- Four months later → reduction in erythema, acne-like eruptions, and beard growth.
Case #5

- Arq Bras Endocrinol Metab 2008;52/7
History

- 54 year old woman
- 4-year history of hair growth, hair loss, acne, amenorrhea, hot flushes and increased libido
- Medical history: P2G2, thyroidectomy for papillary carcinoma
- Familial history unremarkable
- Treatment at presentation: L-thyroxine

Inspired from: Arq Bras Endocrinol Metab 2008;52/7
Physical examination

- Clinical examination
  - BMI 30.4
  - BP 150/98, 98/’
  - Male pattern baldness
  - Acne
  - Grade 15 Ferriman and Gallway score
- Feminine voice, atrophic breasts
- No striae, bruises, acanthosis nigricans
- Pelvic examination
  - Clitoromegaly
  - No adnexal mass
Investigations

- Initial laboratory tests: normal blood count, liver and renal function
- Hormonal evaluation after 8 hours fasting

### Table 1. Hormone levels under basal and dynamic condition and after surgery.

<table>
<thead>
<tr>
<th></th>
<th>Basal hormone levels</th>
<th>ACTH-stimulate hormone levels</th>
<th>30 days after 1st GnRHa administration</th>
<th>30 days after 2nd GnRHa administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (IU/L)</td>
<td>84.2</td>
<td>-</td>
<td>1.1</td>
<td>&lt; 0.6</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>54.0</td>
<td>-</td>
<td>8.6</td>
<td>6.7</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>24.0</td>
<td>-</td>
<td>20.0</td>
<td>&lt; 13.0</td>
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<tr>
<td>Progesterone (ng/mL)</td>
<td>0.3</td>
<td>-</td>
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</tr>
<tr>
<td>Total Testo (ng/dL)</td>
<td>191.0</td>
<td>-</td>
<td>21.0</td>
<td>23.0</td>
</tr>
<tr>
<td>Free Testo (pM/L)</td>
<td>179.0</td>
<td>-</td>
<td>15.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Andro (ng/mL)</td>
<td>3.3</td>
<td>-</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>DHEAS (ng/mL)</td>
<td>1,340</td>
<td>-</td>
<td>1,310</td>
<td>1,110</td>
</tr>
<tr>
<td>Cortisol (µg/dL)</td>
<td>7.1</td>
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<td>17-OHP (ng/mL)</td>
<td>0.7</td>
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60 minutes after the administration of 0.25 mg of ACTH-(1-24) by IV route; 30 days after the administration of 3.75 mg of leuprolide acetate by IM route. LH: luteinising hormone; FSH: follicle stimulating hormone; Total and Free Testo: total and free testosterone; Andro: androstenedone; DHEAS: dehydroepiandrosterone sulphate; 17-OHP: 17-hydroxyprogesterone.
Investigations

- Pelvic ultrasonography
  - right ovary volume 10.3 cc
  - left ovary volume 9.8 cc
  - No nodules or cysts

- Abdominal computerized tomography
  - Normal right adrenal gland
  - Solid 0.8 cm nodule on the left adrenal gland
Differential diagnosis

Cushing syndrome

Primary hyperaldosteronism

Pheochromocytoma

Normal dexamethasone suppression test

Normal K+, aldosterone and plasma renin activity

Normal urinary catecholamines
Treatment

• Exploratory coelioscopy
  • Symmetrically enlarged ovaries, (right ovary 3.0 cm - 10.0 g and left ovary 2.5 cm - 8.0 g), with dense capsules
  • No apparent tumor
  • → Hystero-oophorectomy

• Pathological analysis
  • Hyperthecosis with foci of luteinized stromal cells.
  • Atretic follicles
  • No hilar cell hyperplasia
Differential diagnosis

Cushing syndrome: Normal dexamethasone suppression test

Primary hyperaldosteronism: Normal K+, aldosterone and plasma renin activity

Pheochromocytoma: Normal urinary catecholamines

Ovarian hyperthecosis
Evolution

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- D60
  - Hot flushes, reduced libido and acne
  - Persistant male pattern baldness and hirsutism
• Difficult differential diagnosis in virilizing hyperandrogenic syndromes
  • High prevalence of non secreting adrenal adenoma
• Role of GnRH agonist in determining the origin of hyperandrogenia