An Unusual but Important Cause of Hyperandrogenism in Women

Fatima Alkaabi1, Sara Habboosh1, Ali Abbara1, Karim Meeran1, Jeannine Todt1, Mona El-Bahrawy3, Christina Fotopoulou2, Alexander N Cominios1

1Department of Endocrinology, Hammersmith Hospital, Imperial College Healthcare NHS Trust, UK. 2Department of Histopathology, Imperial College Healthcare NHS Trust, UK. 3Department of Gynaecology, Queen Charlotte’s & Chelsea Hospital, Imperial College Healthcare NHS Trust, UK.

Introduction

- New onset hyperandrogenism in a woman is a rare but important presentation to the endocrine clinic, due to the marked and often alarming effects on the patient, and the variety of causes each with a different management approach.
- Causes of hyperandrogenism in females includes polycystic ovarian syndrome, congenital adrenal hyperplasia, Cushing’s syndrome, ovarian hyperthecosis, and androgen-secreting tumours.

Case Description

- A 61 year-old woman presented with a two year history of worsening facial hirsutism and frontal balding (Figure 1).
- She did not report any deepening of voice, acne, change in body habits or symptoms of Cushing’s syndrome.
- Menarche was at age 14y, with regular menses until a hysterecotsy (with ovarian preservation) for menorrhagia aged 29y.
- She had a past medical history of T2DM and gastric bypass surgery.
- She was not on any androgenic medication.
- Examination revealed clinical hyperandrogenism with hirsutism (FG score 20), androgenic alopecia, and coarse facial features but no clitoromcg pylony.
- There were no clinical features of Cushing’s syndrome or other endocrine disease.
- Secondary sexual characteristics and remaining examination were otherwise normal.
- Blood tests revealed marked biochemical hyperandrogenism:
  - Testosterone 5.7nmol/l (I-2)
  - Androstenedione 1.6nmol/l (I-9)
  - DHEAS 0.8nmol/l (I-0.4-4.7)
  - Oestradiol <70pmol/l
  - LH 22.1IU/l (postmenopausal)
  - FSH 44.3IU/l (postmenopausal)
  - SHBG 27nmol/l (I-30-100)
  - HBc1c 63nmol/mol (20-41)
  - Prolactin, AFP, hCG, IGF1 were within the reference range
- LDDST resulted in suppressed cortisol and DHEAS but no suppression of testosterone, suggesting an ovarian source.
- MRI adrenals and US pelvis were unremarkable with normal-size ovaries (4.1 and 3.1mm).

Clinical Course

- Based on the likely ovarian androgen source with unremarkable US ovaries, she was initially diagnosed with ovarian hyperthecosis and commenced on monthly GnRH-analogue therapy.
- However, on GnRH-analogue therapy, her testosterone levels were still consistently raised (2.3-3.8nmol/l) albeit slightly lower.
- Given the rapidity of the hirsutism, the normal-sized ovaries on US, and the failure to suppress adequately with GnRH-analogues, the diagnosis was re-visited.
- Subsequent MRI pelvis offered superior resolution for ovarian pathology (over previous normal US) and revealed a 1cm left ovarian mass (Figure 2).
- She subsequently underwent laparoscopic bilateral salpingo-oophorectomy and the histopathology identified an ovarian Leydig cell tumour (Figures 3 and 4).

Case Outcome

- Four months post-surgery: Testosterone 0.5mmol/l, LH 2.9IU/l, FSH 10.6IU/l.
- Six months post-surgery her testosterone remains low off LHRH-analogues, with gradual improvement of her hirsutism and stabilisation of her alopca.

Discussion

- The presence of androgen-secreting tumors should be considered carefully when the serum testosterone level is >5.2nmol/l and/or when hyperandrogenism appear abruptly, particularly in postmenopausal women (1-3).
- In addition to the noticeable virilising physical effects of elevated testosterone, hyperandrogenism is also associated with hypercholesterolemia, insulin resistance, hypertension, and cardiac disease as well as the oncological consequences of any tumour. Therefore identification and elimination the source of testosterone is essential (4).
- In premenopausal women, the most common cause of hyperandrogenism is polycystic ovary syndrome. In contrast, when hyperandrogenism develops in postmenopausal women, it is often associated with other causes, such as ovarian hyperthecosis or an androgen-secreting tumour.
- Ovarian hyperthecosis is a disorder characterised by severe hyperandrogenism and insulin resistance. Women usually present with slowly progressive acne and hirsutism (and they are likely to be virilised) (5-7). US usually reveals bilaterally enlarged ovaries (unlike in this patient, which contributed to us questioning the diagnosis).
- Androgen-secreting tumours usually present with rapidly progressive hyperandrogenism resulting in virlisation. These tumours originate from the adrenal glands or ovaries (2).
- Androgen-secreting adrenal tumours are very uncommon, large, aggressive and usually associated with high cortisol levels. However purely androgen-secreting adrenal tumours also exist (2).
- Androgen-secreting ovarian tumours are also rare, representing less than 0.2% of all causes of hyperandrogenism and fewer than 1% of all ovarian tumours (2).
- Sertoli-Leydig cell tumours constitute fewer than 0.5% of ovarian tumors and may be benign or malignant. Crucially they may be small enough to avoid detection even with careful radiological studies leading to bilateral oophorectomy as both a diagnosic and therapeutic approach (2,5,8). This mirrors our case where the tumour was not seen on US but was seen on MRI. In some cases, ovarian sampling can be used to definitively identify the source of the androgens (especially in pre-menopausal women seeking future fertility where unilateral oophorectomy would be preferred).
- Our patient had an elevated testosterone, normal DEHAS and non-suppressible testosterone on LDDST. Her Ultrasound pelvis and MRI adrenals were both unremarkable. She was initially diagnosed with ovarian hyperthecosis but failure of the GnRH therapy to suppress her testosterone into the normal range and her normal-sized ovaries, led us to re-visit her diagnosis. In this case, MRI offered superior resolution of the ovaries and detected a small ovarian tumour.
- Oophorectomy is the treatment of choice (in good surgical candidates) for both ovarian hyperthecosis (bilateral) and ovarian tumours (unilateral)(9,10).

Summary

- Identifying the source of excess androgens is often difficult requiring correct interpretation of symptoms, signs, biochemistry, dynamic testing and imaging.
- In some cases MRI pelvis may offer improved resolution compared to US pelvis and should be considered in difficult cases.

Key references