Virilisation due to a Leydig cell tumor of the ovary – diagnostic and therapeutic challenges

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Introduction

► Frequently encountered in clinical practice (5-10% of women of childbearing age), hirsutism is most often due to polycystic ovary syndrome or it is idiopathic. However rarer causes should be taken into account, such as drugs, congenital adrenal hyperplasia, ovarian hyperthecosis, severe insulin resistance or Cushing's syndrome.

► Severe hirsutism and virilisation, especially if occurring later in life and with rapid onset, should prompt the search for rare but potentially threatening causes such as an androgen secreting ovarian or adrenal tumour.

Presentation

▪ We present the case of PC, 47 years old, who presented to the endocrinology clinic for the investigation of severe hirsutism. At examination she was also found to be obese, with alopecia, acne and deepening of the voice that she declared had appeared insidiously 2 years ago. Although bothersome, she thought these to be a delayed effect of hormonal treatment for fertility during her youth (she was unable to give details).

▪ She declared irregular menstrual periods throughout her life and amenorrhea for the past 2 years, which she interpreted as menopause.

Laboratory evaluation

Haematology and biochemical testing: polycythemia (Haemoglobin= 16.3 g/dl, Haematocrit= 49.3%) and impaired glucose tolerance.

Hirsutism and virilisation:

► IGF1 and 17OHprogesterone were normal, excluding acromegaly and congenital adrenal hyperplasia.

► Baseline ACTH, cortisol and DHEAS levels were normal, with adequate suppression of cortisol after low dose (2x2mg) Dexamethasone suppression testing (LDDST) excluding an adrenal hypersecretion.

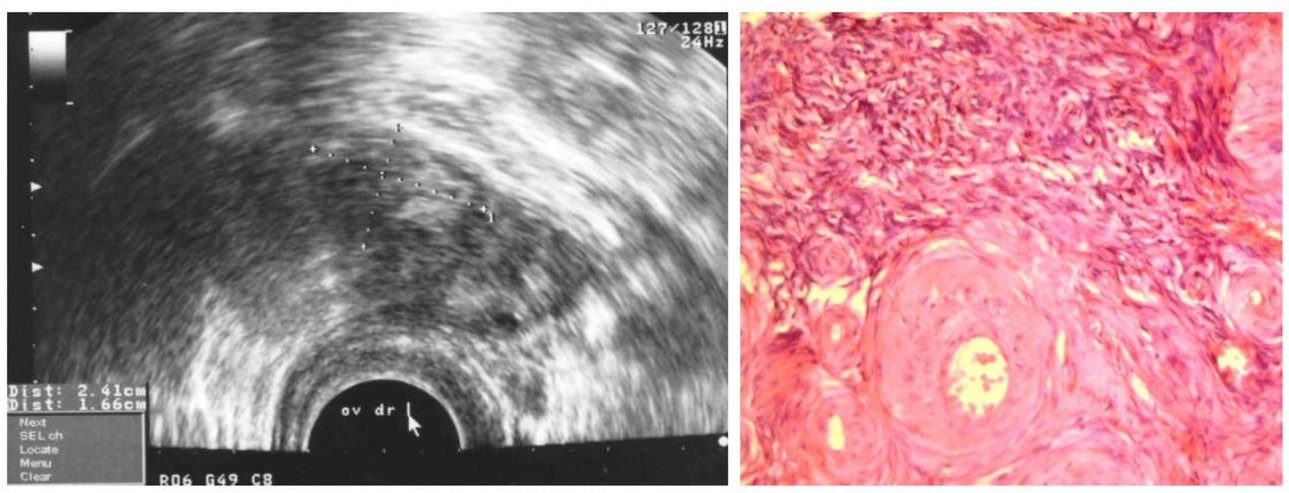

Figure 2. A. Abdominal ultrasound – a 2.41/ 1.66 cm right ovarian mass.
B. Highly vascular ovarian stroma with fragment from a Leydig cell tumor (HE stain, X400)

► **Ovarian sex cord-stromal tumors** are rare neoplasms (~1% of ovarian neoplasms) that develop from the stem cells that would normally generate the cells surrounding the oocytes, including hormone secreting cells. They often secrete androgens and androgen precursors leading to severe hirsutism.

- can be benign or malignant (<20% malignant)
- are usually unilateral and large (>10 cm) unless discovered incidentally
- treatment consists of total hysterectomy with bilateral oophorectomy and surgical staging for women who have completed childbearing

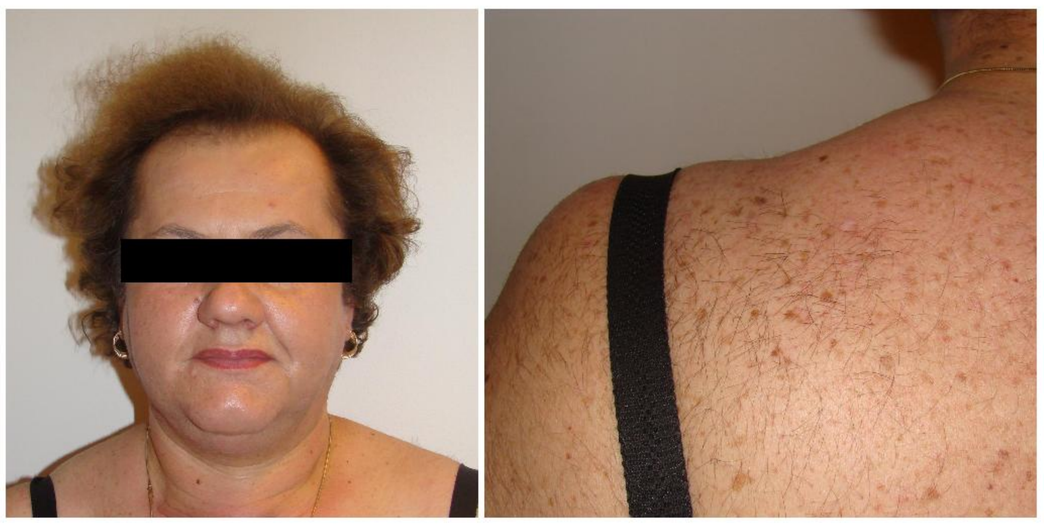

Figure 1. Apr 2013: Frontal alopecia, severe hirsutism, acne

► She had severe hyperandrogenism - total testosterone= 6.38 ng/ml which increased paradoxically after LDDST (7.57 ng/ml)

► Gonadotropins and estradiol were normal (LH=2.63mUI/ml, FSH= 5.59 mUI/ml, estradiol = 86 pg/ml) reflecting either androgen induced amenorrhea in premenopause, or testosterone mediated gonadotropin suppression after menopause.

► CT scans of the abdomen and pelvis and the ultrasound evaluation of the uterus and ovaries showed normal morphology – raising suspicion of ovarian hyperthecosis.

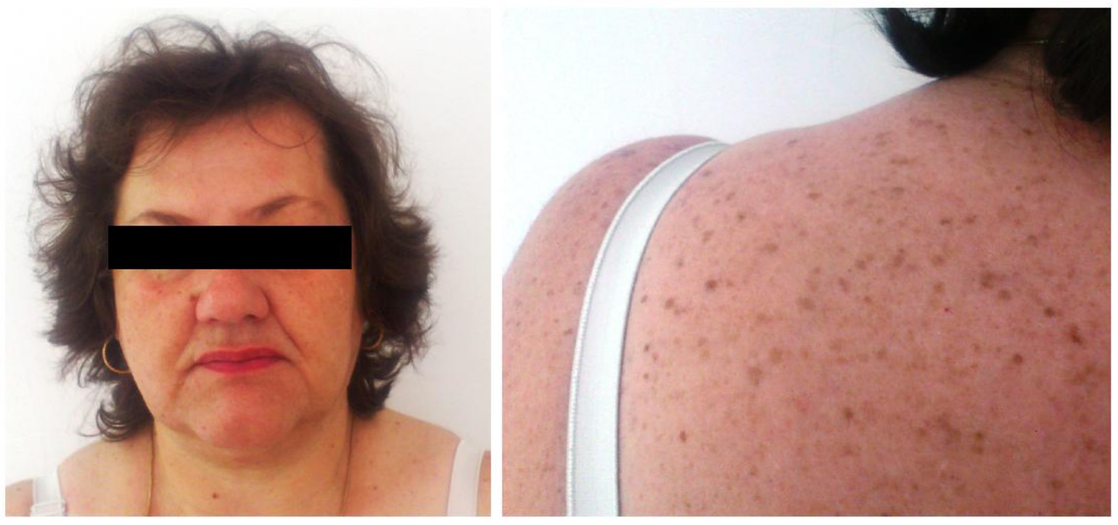

Figure 3. May 2015: Regression of alopecia, and marked improvement of hirsutism

Treatment

Due in part to the lack of clear imaging identifying the cause of the virilization syndrome, the patient initially postponed surgery and **a short trial of GnRH agonist** was attempted (triptorelin 3.75 mg sc per month) with a small decrease in testosterone to 5.65 ng/ml after one month, further proving its ovarian origin.

A repeat ultrasound was performed, showing a 2.41/1.65 cm mass in the right ovary, suggesting an androgen-secreting ovarian tumor.

The patient underwent **bilateral oophorectomy and total hysterectomy** and the pathology report confirmed a benign Leydig cell tumor of the ovary. Testosterone levels normalized imediately post-surgery (0.30ng/ml) and after six months the hirsutism and alopecia were significantly improved, hemoglobin levels normalized, but the obesity persisted and diabetes mellitus was diagnosed.

	Baseline (feb 2013)	Midnight (feb 2013)	LDDST (feb 2013)	After 1 month of treatment with Triptorelin 3.75 mg	Apr 2014	After bilateral oophorectomy	Feb 2014
ACTH (pg/ml)	33.85	-	-				8.53
Cortisol (ug/dl)	10.08	1.6	0.76				9.77
DHEAS (ug/dl)	306.8	-	113.7				191.5
Testosterone (ng/ml)	6.38	-	7.57		5.65		0.33
LH (mUI/ml)	2.63	-	-				12.81
FSH (mUI/ml)	5.59	-	-				27.07
Estradiol (pg/ml)	86	-	-				<20

Insulin resistance and Diabetes Mellitus

Although hyperandrogenism is known to exacerbate insulin resistance (through mechanisms that are still not well defined), in this patient the progression of the impaired glucose tolerance to diabetes mellitus, in the setting of the remission of hyperandrogenism and the presence of obesity, points toward a type 2 DM.

Conclusion:

Although typically large, Sertoli-stromal ovarian tumors can occasionally be small enough to avoid detection even by high-resolution imaging; in the presence of virilization the differential diagnosis includes ovarian hyperthecosis. In either situation bilateral oophorectomy is recommended after the end of childbearing years.

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