

Occult Virilizing Ovarian Tumours in Postmenopausal Women: Problems in Evaluation with Reference to a Case

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Abstract

A 53-year-old postmenopausal presented with hirsutism, acne, receding hairline, male-pattern baldness, and deepening of voice developing over the last five years. Her left ovary had been removed at the age of 38 years old for a benign cyst and vaginal hysterectomy was performed one year later for cervical carcinoma. She had taken premarin 0.625 mg daily since her surgeries. Initial hormonal studies revealed elevated serum concentrations of total testosterone 524 ng/dL (N: 6-86 ng/dL), free testosterone 20.9 pg/mL (N: 0.3-2.7 pg/mL), and 17-hydroxyprogesterone 270 ng/dL (N: <70 ng/dL); but normal baseline concentrations of dehydroepiandrosterone-sulfate, androstenedione, and cortisol. Computed tomographic (CT) scans of the adrenals and ultrasonography of the pelvis were negative. Magnetic resonance imaging (MM) of the abdomen and pelvis similarly were non-revealing. She was given glucocorticoids without effect. Subsequently, retrograde selective venous sampling showed a marked testosterone gradient in the right ovarian vein. A laparoscopic right oophorectomy was performed and a 11 mm Leydig cell tumour of hilus cell type was detected on histologic examination. Postoperative testosterone levels returned to normal and she had slow regression of hirsutism. Our case illustrates that a virilizing ovarian neoplasm can be small and elude imaging studies. We suggest bilateral oophorectomy for postmenopausal women with severe recent-onset virilization and without Cushing's syndrome and with normal adrenal imaging. This approach avoids unnecessary investigations and delays in definitive management.

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Key words: Hilus cell tumour, Hyperandrogenism, Leydig cell tumour, Management, Oophorectomy, Virilizing neoplasm

Introduction

A remarkable variety of endocrinologic disorders may cause virilization syndromes.¹⁻⁶ This can pose a diagnostic dilemma to even the most experienced clinicians. Hirsutism alone is usually innocuous or functional, whereas virilization indicates significant hyperandrogenism, commonly due to an androgen secreting tumour. However, virilization of any degree, regardless of the androgen level, warrants further investigation.⁴ Because of the rarity of virilization syndromes, most clinicians rarely encounter such cases. We report a case of occult virilizing hilus cell tumour of the ovary in a postmenopausal woman.

Case Report

A 53-year-old woman was referred to us for evaluation of hyperandrogenism in February 1996. She first noticed the gradual onset of facial hirsutism five years previously. She was reassured that it was a normal

variant. However, hirsutism progressed fairly rapidly over time and involved her back, chest and abdomen. More distressing, she noticed temporal hairline recession and diffuse scalp hair loss. Meanwhile, she developed deepening of her voice, an increase in musculature and acne. Evaluation of this virilization began in May 1995. These showed a markedly elevated serum total testosterone (582 ng/dL; N: 6-86 ng/dL) and free testosterone (20.9 pg/mL; N: 0.3-2.7 pg/mL); a normal serum androstenedione (1.56 ng/mL; N: 0.10-2.99 ng/mL), dehydroepiandrosterone-sulfate (DHEAS) (45 ug/dL; N: 17-380 ug/dL) and prolactin (6 ng/mL; N: 5.0-22.6 ng/mL).

Her other medical history included hypertension of 20 years duration, under treatment with captopril 25 mg twice daily and prazosin 2 mg twice daily. She also had a 20-year history of type 2 diabetes mellitus, treated with insulin for the past 10 years. She gave a history of a benign left ovarian cyst, treated by left salpingo-

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oophorectomy in 1980. Stage II cervical carcinoma was diagnosed in the following year and treated with a total vaginal hysterectomy. She believed that a right oophorectomy had been performed during that procedure; however, records of that surgery were not immediately available. Her menarche was at age 13 and she had normal menstrual cycles with four successful pregnancies prior to her surgeries.

The patient was seen by an endocrinologist in June 1995. Examination revealed virilization but no cushingoid features. A random morning serum cortisol level was normal (9 ug/dL; N:2-25 ug/dL). An abdominal computed tomographic (CT) scan showed normal adrenal glands. Pelvic imaging was not performed initially due to the belief that she had had a bilateral oophorectomy. Repeat measurements for total and free testosterone levels remained elevated. At this point, due to the absence of an identifiable tumour, a diagnosis of functional adrenal hyperandrogenism was made. She was found to have an elevated basal 17-hydroxyprogesterone (17-OHP) of 242 ng/dL (N:<70 ng/dL), so a diagnosis of partial 21-hydroxylase deficiency was considered. Dexamethasone was prescribed for adrenal suppression. While receiving dexamethasone 0.5 mg daily for four weeks, her serum testosterone rose slightly to 769 ng/dL. Because of concern regarding the accuracy of her dosing with dexamethasone liquid, hydrocortisone tablets 20 mg every morning and 10 mg in the evening was given. A repeat serum testosterone a month later was 574 ng/dL. Due to a lack of clinical response, dexamethasone was reinstituted at a higher dose (0.75 mg daily), which aggravated her diabetes. In December 1995, she was found to have had a unilateral ovarian resection; however, a pelvic ultrasound failed to show either an ovary or an adnexal mass, and a CT scan confirmed the absence of the uterus and showed neither an ovary nor a pelvis mass.

Despite glucocorticoid treatment, the patient had progressive hirsutism until, by February 1996, she was spending an hour daily removing facial hair. Examination revealed a heavy-set Caucasian woman with a relatively muscular physique and a deep voice. She had moderate hirsutism of her face, chest, back and abdomen, as well as diffuse scalp alopecia and temporal hairline recession. She had a male-pattern escutcheon and a prominent clitoris. She had no cushingoid features or acanthosis nigricans. Further endocrine testing showed the following results: total testosterone 864 ng/dL; 17-OHP 270 ng/dL; 11-deoxycortisol (11-DOC) 0.05 ng/dL (N: <120 ng/dL); deoxycorticosterone 8.0 ng/dL (N: 3.5-11.5 ng/dL); follicle stimulating hormone (FSH) 18.6 mIU/mL; luteinizing hormone (LH) 14.0 mIU/mL (on premarin 0.625 mg daily). Apart from erythrocytosis [haemoglobin (Hgb) 18 g/dL and haematocrit (Hct) 52.6%], she had normal blood counts, serum electro-

lytes, liver and renal function tests. After discontinuation of corticosteroids, her diabetes was well controlled with HbA1c of 5.87% (N: 4.4%-6.4%).

A repeat pelvic and vaginal ultrasound was performed at our centre; a right ovary measuring 8 mm was noted. There were no adnexal masses, and no uterus or left ovary was visualised. Meanwhile, dexamethasone was discontinued and she was treated with spironolactone 100 mg twice daily which appeared to slow the progression of the hirsutism. Magnetic resonance imaging (MRI) of her abdomen and pelvis failed to yield additional information. The patient then underwent a percutaneous selective venous catheterisation for total and free testosterone determinations. As shown in Table I, these values were markedly increased in the right ovarian vein at 41780 ng/dL and 22 728 ng/L, respectively.

She underwent laparoscopic right oophorectomy in August 1996. Intraoperatively, the right ovary appeared slightly larger than a normal postmenopausal ovary. On pathological examination, it contained a soft fleshy brown hilar nodule measuring 11 × 9 × 6 mm. Microscopically, the nodule exhibited the features of a Leydig cell tumour of hilus cell type. The nodule was circumscribed, but not encapsulated (Fig. 1) and was composed of polygonal cells with round or irregular nuclei containing small nucleoli. Some cells contained round eosinophilic intracytoplasmic hyaline globules and rod-like structures compatible with crystalloids of Reinke (Fig. 2). Her serum testosterone level measured one week after the resection was normal at 20 ng/dL. She continued on spironolactone treatment and has noted gradual improvement in her hirsutism.

Discussion

Causes Of Hyperandrogenism

Postmenopausal hyperandrogenism has a variety of aetiologies, which includes androgen production from either neoplastic or non-neoplastic conditions. A summary of the causes of virilization is presented in Table II.

TABLE I: SELECTIVE VENOUS SAMPLING DATA

Location	Total testosterone (ng/dL) (norm: 15-70)	Free testosterone (ng/L) (norm: 1.0-8.5)
IVC-suprarenal	672	96.3
IVC-infrarenal	525	69.5
adrenal-right	651	118.5
adrenal-left	517	75.0
renal-right	519	77.2
renal-left	564	81.4
ovarian-right	41,780	22,728.0
iliac-right	508	77.3
iliac-left	450	67.1
brachial-left	543	80.2

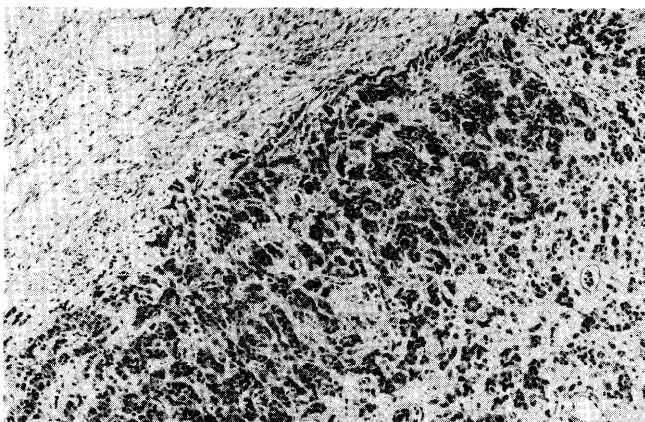


Fig. 1. The tumour, located in the hilum of the ovary (bottom right), is circumscribed but not encapsulated (H&E; $\times 40$).

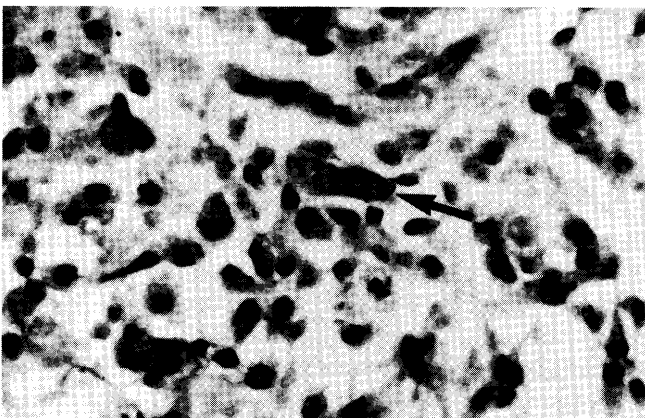


Fig. 2. The tumour cells are plump with round or oval dark-staining nuclei and abundant eosinophilic cytoplasm. One of the tumour cells contains an elongated eosinophilic intracytoplasmic crystalloid of Reinke (arrow) (H&E; $\times 100$).

Androgen secreting neoplasms are either of adrenal or ovarian origin. Virilizing adrenal neoplasms are commonly sizeable tumours often readily diagnosed by high-resolution CT or MRI studies, the prototype being the adrenal carcinoma.⁶⁻⁸ Virilizing ovarian tumours form a heterogeneous group with rather complex histologic classifications.¹⁻⁴ The hilus cell tumour occurs predominantly in postmenopausal women and this can be notable for being relatively minute in size.^{2,9,10} Such tumours are very rare and are almost always benign in nature.^{2,3} Premenopausal women with virilizing ovarian neoplasms more commonly have either Sertoli-Leydig cell tumour (arrhenoblastoma) or steroid cell (lipoid cell) tumour. Both are usually relatively large tumours with greater propensity for malignancy than the hilus cell tumour.^{1,11}

Adrenocorticotrophin (ACTH)-dependent Cushing's syndrome, polycystic ovarian disease or late-onset congenital adrenal hyperplasia can all contribute to functional adrenal hyperandrogenism.⁵ Functional ovarian causes include polycystic ovarian disease, stromal hyperplasia and hyperthecosis, or stromal reaction to non-

TABLE II: CAUSES OF HYPERANDROGENISM AND VIRILIZATION

A. Adrenal Pathology	
Functional	
ACTH-dependent	Cushing's syndrome
Congenital adrenal hyperplasia*	
Polycystic ovarian disease	
Neoplastic	
Adrenal adenoma	
Adrenal carcinoma	
B. Ovarian Pathology	
Functional	
Stromal hyperplasia/hyperthecosis	
Polycystic ovarian disease	
Massive ovarian oedema	
Pregnancy associated (leutoma, hyperreactio luteinalis)	
Neoplastic	
Sertoli-Leydig cell tumour	
Leydig cell tumour (hilus cell type)	
Steroid (lipoid) cell tumour	
Functional stroma secondary to non-secreting tumours	
Germ cell tumours	
Ovarian metastatic deposits	
C. Drugs	
Anabolic steroids	
Progestogens (19-norsteroid derivatives)	
Danazol	

ACTH: adrenocorticotrophin

* Includes deficiency of the following enzymes: 21-hydroxylase (commonest), 11-hydroxylase and 3-beta-hydroxysteroid-dehydrogenase.

functioning ovarian tumours.^{3,4,12} The polycystic ovarian disease is a clinical diagnosis based on the coexistence of chronic anovulation and varying degrees of hirsutism, which usually become evident around the time of expected menarche. Hyperandrogenism arising from ACTH-dependent Cushing's syndrome commonly manifest hirsutism, acne, seborrhoea and thinning of scalp; whereas temporal balding or overt signs of virilization are rare.¹³ Non-functioning ovarian tumours which are benign or malignant, primary or metastatic, can also stimulate the adjacent stroma or hilus cells to produce androgens and/or other steroid hormones.¹² Hyperandrogenism in these conditions often regress after treating the primary pathology.

Clinical Features of Virilization

An important feature in the history is the rapidity of onset of virilization: a rapidly progressive course is particularly worrisome, as in our patient.⁴ In general, defeminizing signs are first noted as androgen levels increase in the circulation over several months. This includes loss of female body habitus and decreased breast size, although such features are less conspicuous in postmenopausal women. This is followed by acne, seborrhoea and hirsutism. Finally, frank

masculinization and virilization develops. Virilizing features include deepening of the voice, temporal balding and clitoromegaly. Menstrual irregularities often occur in premenopausal women, whereas some postmenopausal women may also experience unexplained bleeding.

Hormonal Evaluations and Interpretations

Serum androgen measurements provide biochemical confirmation in all women with virilization. Elevated levels of testosterone usually imply an ovarian source, whereas elevated levels of precursors like DHEAS and androstenedione usually imply an adrenal source. However, exceptions are not uncommon, as no androgen is produced exclusively by the adrenal gland or the ovary.^{4,6,8,14} Generally, an androgen-secreting tumour is suspected if testosterone levels are greater than two to three times the normal range, although much overlap with functional states exist.^{3,4,9} Further investigations are necessary if virilization is present, even if serum testosterone levels are not markedly elevated. In equivocal cases, determination of free testosterone may be useful to exclude abnormal sex-hormone binding globulin (SHBG) levels; the latter can be elevated by estrogens or thyroid hormone and suppressed by androgens, glucocorticoids, growth hormone or obesity.¹⁵

Marked hyperandrogenaemia in our case suggested an androgen-secreting adrenal neoplasm due to her apparent history of prior bilateral oophorectomies. In view of negative imaging studies, functional hyperandrogenism was considered. Unfortunately, measurement of 17-OHP led to an erroneous diagnosis of late-onset congenital adrenal hyperplasia (CAH). Although this condition is being increasingly recognised in adulthood, these women usually present in their reproductive years with impaired fertility, polycystic ovarian syndrome or simply hirsutism.^{5,16} In retrospect, CAH would be extremely unlikely to cause a rapid onset of virilization in a postmenopausal woman. As steroidogenic cells of the gonads and adrenals are capable of synthesizing various hormones or precursors, serum levels of 17-OHP may be elevated with either ovarian or adrenal neoplasms.¹⁷

As virilizing adrenal tumours usually secrete significant quantities of androgenic precursors, the finding of isolated testosterone elevation in our case favours a diagnosis of ovarian hyperandrogenism, although exceptions do occur.^{6,18} Conversely, ectopic cortisol production has been reported in women with virilizing ovarian lipid cell tumours, presumably of adrenal rest origin.^{19,20}

Role Of Perturbation Studies

Perturbation studies provide a functional assessment of hyperandrogenism: this involved the use of

corticosteroids and gonadotropin-releasing hormone (GnRH)-agonists to suppress androgen production from adrenal and ovarian sources respectively, or the use of ACTH and human chorionic gonadotropin (hCG) to stimulate androgen production from adrenal and ovarian sources respectively. However, results from such studies can be extremely variable and lead to erroneous conclusions.^{4,6,14,18} Furthermore, women with functional causes often have mixed sources of androgen excess and their androgen secretion can be episodic.²¹ Our patient showed no reduction in testosterone levels with corticosteroid treatment, but this was judged as possibly being due to inadequate dosing which led to an escalation of her glucocorticoid dose, thus aggravating her diabetes.

Imaging Studies for Tumour Localisation

The next step in the diagnostic approach to virilization is to exclude the presence of a tumour in the adrenal or ovary via imaging studies. Androgen-secreting adrenal tumours are usually readily visualised on high-resolution CT or MRI.⁶⁻⁸ The finding of normal adrenals, as in our case, generally excludes an adrenal neoplasm. A caveat, however, is that non-functioning adrenal tumours may be discovered incidentally in up to 5% of routine abdominal CT scans.²² Concurrent study of both the adrenal and ovarian anatomy is therefore necessary to avoid such a diagnostic pitfall. Rarely, an androgen-secreting lipid cell tumour may be located ectopically, such as in the broad ligament.²³

Pelvic ultrasonography, especially with a transvaginal transducer, is the preferred imaging modality for the ovaries, as it affords superior sensitivity compared to the more costly CT or MRI.²⁴ Our case illustrates the difficulties encountered with imaging studies to delineate such small lesions. In the premenopausal women, small ovarian tumours may likewise be difficult to identify in polycystic ovaries.

Functional Radionuclide Scintigraphy

Iodomethyl-norcholesterol (NP-59) scanning, employing radiolabelled cholesterol to depict functional steroid hypersecretion, has been advocated for the localisation of virilizing neoplasms. This was reported to be the single most useful localisation study in a small series, providing definitive results in 5 of 7 patients with virilization.²⁵ However, results of iodocholesterol scanning to detect adrenocortical tumours have been generally inferior to CT or MRI.²⁶ Nevertheless, scintigraphy may be useful in special cases, including patients with metallic clips in situ, and in those with suspected ectopic tumours.

Selective Venous Sampling

Percutaneous selective venous catheterisation is gen-

erally recognised as the definitive tool if other tumour localisation procedures were unsuccessful.^{9,10,27} This technique clearly has its utility, especially in the premenopausal women whereby preservation of fertility is desirable. Patients with virilizing tumours are expected to have lateralization of the androgen gradient, as opposed to those with functional hyperandrogenism. Selective venous sampling was successfully performed in our patient with elegant demonstration of unilateral testosterone gradient in the right ovary (Table I). The interpretation of sampling results, however, can be difficult at times, as illustrated by the occasional reports of bilateral hilus cell tumours.²⁸ This remains an adjunctive method as a high degree of expertise is required in selective catheterisation studies.^{4,9}

Treatment and Outcome

In postmenopausal women, a bilateral oophorectomy will eliminate hyperandrogenism due to ovarian causes, regardless of pathology or laterality. In retrospect, prompt oophorectomy would have avoided many investigations in our patient and would have eliminated her hyperandrogenism more quickly. In such instances, selective venous catheterisation studies are unnecessary. Our patient had complete resolution of hyperandrogenism after surgery and her prognosis is excellent, as the hilus cell tumours are nearly always benign.^{2,3,28} However, virilization from longstanding hyperandrogenism seldom regress fully.

In summary, a case of an occult virilizing ovarian tumour is reported to illustrate the complex and challenging diagnostic evaluation. In the postmenopausal women, we suggest a simplified approach with bilateral oophorectomy if the presence of adrenal lesion is excluded.

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