Secondary hypertension and hirsutism as a clinical manifestation of tumor duplicity

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Background. The differential diagnosis of the pathogenetic causes of hirsutism in combination with hypertension is a challenge for clinicians.

Methods and Results. This case report demonstrates a patient suffering from two hormonally active tumors – an adrenal adenoma with primary aldosteronism and a Leydig cell ovarian tumor with hyperandrogenism. The task of the authors was easier due to the perimenopausal age of the proband. Adrenal selective venous sampling was very helpful in the diagnosis of these active endocrine tumors. Both were resolved by a single laparoscopic surgery.

Conclusion. The combination of the two described tumors is a unique clinical finding. The resolution using laparoscopy in a single procedure provided an elegant and efficient therapeutic approach.

Key words: hirsutism, secondary hypertension, aldosterone-producing adenoma, Sertoli-Leydig cell tumor

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INTRODUCTION

Many subtypes of primary aldosteronism have been described since Conn's original report of the aldosterone-producing adenoma in 1954 (ref.¹). Adrenal tumors are a rare cause of androgen excess. A few are adrenal adenomas that secrete mostly testosterone, but most are carcinomas that often secrete not only androgen, mostly DHEA and DHEA-S, but also cortisol. Hirsutism caused by an androgen-secreting tumor is most likely to occur later in life. Androgen-secreting tumors constitute only 5 percent of all ovarian tumors; histologically they are Sertoli-Leydig

cell tumors (androblastoma, arrhenoblastoma), granulosa-theca cell (stromal cell) tumors, and hilus-cell tumors. Many of these tumors can be identified by transvaginal ultrasonography.

CASE REPORT

A 53 year old female (98 kg, 158 cm), 2 children, had no health problems until the age of 43, when she was revealed to have poorly controlled hypertension between 160-170/90-95 torr. Her periods stopped at 47, which

Fig. 1. Before the treatment. Typical picture of hirsutism (A). Half a year after the surgical procedure (B). Nearly perfect retreat of hirsutism.

was considered to be a natural menopause. Almost immediately pronounced hairiness of her whole body followed. Based on the evaluation of hirsutism according to Ferriman-Gallwey scale it was possible to unambiguously assign the patient with a score 36 (Fig. 1A). Neither acne nor seborrhea was present. In a short time the problem forced her to undergo cosmetic depilation of the exposed parts of her body, but the intensity and extent of the effect was insufficient. In her 50th year she manifested adult-onset type 2 diabetes mellitus. Hypertension was partially controlled with an ACE inhibitor and calcium blocker. Diabetes mellitus was satisfactorily treated with glimepiride and metformin. Both pheochromocytoma and hypercortisolism were excluded. On the other hand, the blood tests, namely the activity of plasmatic renin and aldosterone confirmed the diagnosis of primary hyperaldosteronism. Computed tomography scan revealed a small tumor of the right adrenal gland of low density and diameter about 20mm. Plasma testosterone levels in peripheral blood reached 27.9 nmol/L (physiological range 0.5-3 nmol/L). Androstenedione 8.76 nmol /L (physiological range 1.25-6.28 nmol/L) was very slightly elevated, too. Free androgen index reached 62.2 (normal range up to 8). Dehydroepiandrosterone sulphate levels, sex hormone binding globulin and 17-hydroxyprogesterone were all repeatedly within physiological range. Selective adrenal veins sampling² enabled reliably locate the source of aldosterone excess into the right adrenal gland (Table 1). Therefore, androgens secreting tumor of the ovary glands was searched for, and confirmed by transvaginal sonography on the ipsilateral (right) side. Ovarian venous sampling was not considered necessary due to the patient's age³. The urologist performed right-sided laparoscopic adrenalectomy and the gynecologist added bilateral resection of the ovaries and fallopian tubes at one time. Mere gross examination confirmed the expected both right adrenal and ovarian tumors. In the right adrenal cortex, there was an obvious focal adrenal hyperplasia 7x7 mm in diameter. The right ovary was about 35x30x25 mm. The samples showed well circumscribed tumor embedded within the ovary approximately 15 mm in diameter. Both specimens were routinely processed

and sections stained with hematoxyline-eosin. There was found focal adrenocortical hyperplasia of the zona glomerulosa cells, sometimes admixed with fascicular cells typical for adrenal cortex (Fig. 2). Microscopic examination of sections of right ovarian tumor revealed solid growth of polygonal Leydig cells with abundant acidophilic cytoplasm in fibrous stroma without mitotic figures (Fig. 3). The most helpful immunohistochemical findings of the primary Leydig cell tumor were as follows: negative staining of tumor cells for epithelial membrane antigen, AE1/3, SMA and S-100, and positive stain for inhibin. A thorough check of the patient one month after the surgical procedure revealed normalization of all initial pathological laboratory parameters. Originally low gonadotropin levels reached high limits common in menopausal women. After the surgical procedure her blood pressure dropped to 125/80 during the first month and the whole body hirsutism retreated during the next 3-5 months (Fig. 1B).

DISCUSSION

Primary aldosteronism is not rare after the exclusion of renovascular hypertension. Hirsutism is also a quite common challenge. A very important factor which allows deduction of the significance of this clinical image is the speed with which hirsutism occurs, and the testosterone plasma level⁴. In many cases of idiopathic hirsutism, the cause cannot be determined. For clinical purposes it is always useful to divide the other conditions that cause abnormal growth of terminal hair into two categories, androgen and non-androgen related. Hypothyroidism predisposes to hirsutism as well as the hyperandrogenic variant of insulin-resistant syndrome, acantosis nigricans, classical and non-classical form of 21-hydroxylase deficiency as well as block of 11beta-hydroxylase and hypercortisolism. Hirsutism accompanies ovarian hyperthecosis and the polycystic ovary syndrome. As for the androgenic profile it should be stressed that DHEA-S is produced solely by the adrenal gland at a rate of 3.5 to 20 mg per day. Such low levels of DHEA-S in peripheral blood identify unequivocally the source of androgens to the ovary. The case

Table 1. Preoperative adrenal veins sampling results.

Methods	Catheter position		
	Inferior vena cava	left	Suprarenal vein right
ALDO	156	1500	1500
PRA	0.27	0.31	0.18
ALDO/PRA	57.80	483.90	833
S-cortisol	532	1380	1380
Testosterone	27	29.8	39.60
ADIO	8.76	35.43	35.40
DHEA-S	5.49	9.73	11.50

Physiological ranges

Aldosterone (ALDO) basal 8-172 ng/L, plasmatic renin activity (PRA) basal 0.5-1.9 ng/mL/h, ALDO/PRA 0.00-30.0, S-cortisol 330-710 nmol/L, testosterone 0.5-3.8nmol/L, adrostendione (ADIO) 1.25-6.28nmol/L, dehydroepiandrosterone sulfate (DHEA-S) 1.5-7.7umol/L.

Fig. 2. The adrenal tumor is characterized by solid growth of polygonal cells with an abundant acidophilic cytoplasm. Hematoxyline-eosin, 100x.

Fig. 3. Leydig cell tumor presents the sharply delimited solid nodule embedded within the ovary. Hematoxylin-eosin, 40x.

is interesting because of the duplicity of the two hormonally active tumors resulting in successful laparoscopic solution of adrenal-ovarian problems in a single surgery. The presence of both hormonally active adrenal adenoma and virilising tumor of the ovary histologically corresponding to rare benign ovarian tumor of Leydig cells has not been described to date. Postoperative laboratory check confirmed that the clinical reasoning was correct, and the indicated procedures were justified. Both plasma renin activity and aldosterone as well as serum testosterone levels normalized completely. Noteworthy is also the fact that the originally relatively low levels of gonadotropins (FSH 6.9 IU/L, LH 3.7 IU/L) increased to values common in menopausal women, specifically FSH 21.9 IU/L, LH 11.9 IU/L. The postoperative gonadotropin increase closely followed full normalization of testosterone that indirectly confirmed the completeness of the radical surgical treatment. The situation was quite easy to solve because there was no need to preserve a functioning ovary. The authors found several articles describing concurrent occurrence of ovarian and adrenal tumors in the literature but no combination of primary hyperaldosteronism and Leydig cell tumor so far^{5,6}.

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