Arrhenoblastoma of the ovary with virilism
A case report with hormonal study

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An intermediate type arrhenoblastoma of the left ovary in a 25-year-old infertile woman is reported, in association with a
teratoma. Basal plasma testosterone was markedly elevated. It rose under attempts at dexamethasone inhibition, and declined
under norethindrone therapy. Following surgery the patient improved in her virilizing syndrome, resumed spontaneous menstrua-
tion and became pregnant. The histologic and hormonal characteristics of this case and correlated and discussed leading to the as-
sumption that the ovarian stromal reaction rather than the tumor itself is the source of testosterone.

plasma testosterone; dexamethasone inhibition; norethindrone therapy

Introduction

Arrhenoblastoma is a rare potentially malignant ovarian tumor, predominantly unilateral, that is re-
sponsible for metastases or recurrences in 12 to 22% of the cases (Javert and Finn, 1951). The average age of
occurrence ranges between 29.7 and 34.2 years (Hertig and Gore, 1961) and its coexistence with a
masculinizing syndrome is not infrequent.

Several theories have been proposed to explain the histogenesis of this tumor, among which the possibility
that the neoplasm may arise from teratomas, although such views are not shared by many investiga-
tors because of lack of support (Hughesdon and Fraser, 1953).

The histologic pattern of these tumors is variable. Among 114 cases of arrhenoblastoma of the ovary
studied by Hughesdon and Fraser, they found 13 of the tubular type, 25 intermediate and 76 atypical
(Hughesdon and Fraser, 1953).

The purpose of this presentation is the discussion of one arrhenoblastoma of the intermediate type
associated with a teratoma in a severe virilized infertile patient who was submitted to hormonal studies,
before and after surgery, and subsequently became pregnant.

Case report # 3921

M.I.E. white female, 25 years of age; married for the past five years; primary infertility. She had her
menarche at the age of 13. The subsequent menstrual cycles were regular up to the age of 15 years. Then
she developed oligomenorrhea and had an amenorrhea of five months' duration. Between the age of 17
and 18 the patient had spontaneous regular menstrual cycles. Then, and up to the present time, a longstanding
amenorrhea began. Hirsutism had its onset at the age of 21 and became more and more pronounced.
There was a weight gain of 9 kg (20 pounds). Her initial infertility investigation showed a monophasic hypothermic basal body temperature pattern. An endometrial biopsy disclosed a proliferative endometrium while she was already amenorrheic. She had uterine withdrawal bleedings with progestrone. A tubal air insufflation was normal. The husband’s semen was within the normal range. An attempt to induce ovulation was made with clomiphene citrate (500 mg per cycle) without success. In view of her hirsutism and a pelvic examination showing enlarged ovaries she was referred to the senior author for investigation.

She weighted 67 kg and had a blood pressure of 135/85 mm Hg.

The hirsutism was very pronounced, all over the body, with a male escutcheon (Fig. 1); the patient

Fig. 1. Hirsutism. Left: before operation. Right: five months after operation.

Fig. 2. Breast development. Left: before operation. Right: five months after surgery; besides a decrease in hair, there was an increase in breast volume.
had to shave frequently. The breasts were large and well developed with normal palpable gland (Fig. 2). There was no discharge by the nipple. The clitoris was markedly enlarged and measured 1.5 cm in length (Fig. 3). On pelvic examination the uterus was normal in size, with normal cervical mucus flow. The left adnexa contained a cystic, 6 cm diameter, nontender, mobile mass.

A flat X-ray film of the abdomen did not show any structures with bone density in the area of the palpable adnexal mass. Papanicolau smear of the cervix: negative (type I). Blood studies: RBC 4,350,000/ml; WBC 5,900/ml; hemoglobin 12 g%; differential count: neutrophils 56%, eosinophils 4%, lymphocytes 38%, monocytes 2%. Erythrocyte sedimentation rate 3 mm (Westergreen). Blood urea 30 mg%; glucose 85 mg%; sodium 140.5 mEq/l; potassium 4.55 mEq/l. Urinalysis was normal. A culture was negative.

An initial hormonal study was done. Total urinary estrogens: 38.7 μg/24 h; pregnanetriol 3.1 mg/24 h (normal 0.2–2.4 mg/24 h); 17-ketosteroids 11 mg/24 h (normal 5–15 mg/24 h); total 17-hydroxysteroids 13.7 mg/24 h (normal 5–15 mg/24 h); dehydroepiandrosterone 1.1 mg/24 h (normal 0–2 mg/24 h); radioimmunoassayable plasma FSH 2.2 mIU/ml and plasma LH 8.7 mIU/ml; plasma testosterone 280 ng/100 ml (normal 20–80 ng/100 ml).

A suppression with dexamethasone (2 mg/day) alone or in combination with norethindrone acetate (5 mg/day) was undertaken (Fig. 4).

In view of these data it was decided to perform a laparoscopy prior to surgery. This examination showed very clearly a large and abnormal left ovary. Under the same anesthesia a left oophorectomy and salpingectomy was performed. A right oophorectomy was done for inspection; as a result this ovary was considered normal and sutured. There were no nodes or fluid in the peritoneal cavity. The liver was normal. The patient had an uneventful postoperative period and was discharged at the end of one week.
A postoperative hormonal study two weeks later showed a normal plasma testosterone (80 ng/100 ml). One month after surgery the patient had a spontaneous menstruation for the first time in 7 years. The hirsutism was less marked. At a last examination, seven months after surgery, she was already pregnant (seven weeks' gestation); fetal heart movements were positive by ultrasound. The right ovary was not palpable. The hirsutism was less marked and she shaved less frequently. Plasma testosterone was 108 ng/100 ml.

Following surgery and up to the time she became pregnant she had four normal menstruations with regular cycles and biphasic basal body temperature records.

Pathology report

Cross-examinations

The excised part is both the ovary and tube (Fig. 5). The ovary measured 9 × 5 × 5 cm with its greatest diameter parallel to the tube. Its external surface is smooth and slightly bosselated in the extremity close the distal end of the tube, corresponding to small cystic cavities, the largest of which measured 2 cm in diameter and has clean contents and smooth walls. In the remainder of the longitudinal section (Fig. 6) one can see a white-pink nodule, not very hard, measuring 4 × 5 × 5 cm, adjacent to which there are several similar but smaller nodules.

Microscopic examination

The histologic pattern varies from field to field. The above mentioned nodules are composed of nests...
of large polygonal or round epithelial cells, arranged in cords separated by very small capillaries (Fig. 7). One can also see a few gland-like structures, as tubules with a narrow lumen, surrounded by the same cells (Figs. 8, 9). In some zones of the stroma, where the tissue is looser, a high power view of these cells (Fig. 10) shows sharp cellular membranes, small nuclei and spongy cytoplasm finely vacuolated, containing lipoid material (Sudan positive). These luteinized ovarian cells are very similar to Leydig cells. The nodules are not encapsulated and there are no sharp boundaries between the tumor and the adjacent ovarian stroma (Figs. 8, 9). The cystic cavities are lined by a flat columnar epithelium; near them there is an extensive zone with abundant glands, often dilatated, where a columnar epithelium and goblet cells can be visualized (Fig. 11). This epithelium and the product of secretion contained in the glandular lumen are strongly mucicarminophilic. Some regular mitotic figures were seen, particularly in the nodules. There is no microscopic evidence of malignancy.

Fig. 6. (Reg. NS-No. 22245): Longitudinal section of the ovary. White-pinkish nodules in the tumor. To the left there are cystic cavities.

Fig. 7. (Reg. NS-No. 22245): Cords of round or polygonal epithelial cells separated by capillaries. Hematoxylin & eosin; ×250.
Fig. 8. (Reg. NS-No. 22245): Scattered Leydig-like cells and a tubular pattern. Hematoxylin & eosin; ×250.

Fig. 9. (Reg. NS-No. 22245): Tubular pattern. Leydig-like cells scattered in the stroma. Hematoxylin & eosin; ×250.
Fig. 10. (Reg. NS-No. 22245): Leydig-like cells with sharp membranes and vacuolated cytoplasm. Hematoxylin & eosin; ×450.

Fig. 11. (Reg. NS-No. 22245): Glands with columnar epithelium, goblet cells and clumps of mucin.
Pathology diagnosis

Multinodular arrhenoblastoma of the ovary, of the intermediate type, with rare tubular zones and a predominance of nonsarcomatoid solid structures associated with a teratomatous ovary.

Discussion

This clinical case has several aspects that deserve consideration, the first one being the time of onset of the symptomatology. It seems that this tumor started secreting androgens suddenly (seven years prior to surgery), when the patient developed a secondary amenorrhea, since in the year before the onset of symptoms she had had spontaneous regular cycles that lasted 12 months. A stronger hormonal effect was manifested three years later, after the establishment of amenorrhea, when hirsutism became apparent.

The second interesting aspect is the fact that even under such an intensive and longstanding suppression with a strong androgen, the hypothalamus was not functionally damaged. It resumed an entirely normal cyclicity, the proof of which is the quickly achieved pregnancy as often reported in the literature (Javert et al., 1951).

The third important feature of this case centers around the classical discussion of the histogenesis of arrhenoblastomas (Iverson, 1947; Novak and Long, 1965). Although the hypothesis implicating a teratoma in the etiology of this tumor is generally considered to be devoid of support, there is no doubt that both entities can at least be associated suggesting a possible interrelationship, as in the present report. Dr. Edmund Novak kindly reviewed the sections and confirmed our opinion that “this does represent a gonadal stromal tumor probably in conjunction with a benign teratoma, because there are obvious mucinous areas as well as several areas of rather definite and profound proliferation of ovarian stroma producing areas of apparent hyperthecosis” (Novak, E.R., personal communication).

The histologic pattern of this arrhenoblastoma is not the commonest. Dr. Novak stated that “the tumor is not very well differentiated and there is a very large number of interstitial cells, which is in accord with the rather marked degree of virilism” of this patient (Novak, E.R., personal communication).

The correlation of the histologic findings with the hormonal studies and the clinical picture of this patient offers an interesting opportunity to speculate about the probability of an intrinsic hormonal activity of such tumors.

There is, in this case, a “profound proliferation of ovarian stroma producing areas of apparent hyperthecosis”, “a very large number of interstitial cells which is in accord with the rather marked degree of virilism”. We were the first to demonstrate that in hyperthecosis associated with virilism, rather than hirsutism, there is a high level of plasma testosterone (Neves-e-Castro, Neves da Silva and Reis-Valle, 1963) as confirmed by other authors (Bardin, Lipsett, Edgecomb and Marshall, 1967).

On the other hand, we have already reported (Neves-e-Castro et al., 1963) one case of a severely virilized patient who had a cystadenocarcinoma of the ovary associated with marked hyperthecosis, indicating that the peritumoral stroma is the probable source of androgens. In addition, there are many reports in the literature of other nonendocrine tumors of the ovary associated with virilism, as is the case of Krukenberg’s and Brenner’s (Scully and Richardson, 1961) the common denominator among them being the presence of marked stromal reactions.

Conversely, hyperthecosis or stromal luteinization per se are reported in association with defeminization or virilization (Bardin et al., 1967; Scully and Richardson, 1961; Geist and Gaines, 1942; Schneider, 1942; Hughesdon, 1958; Jones, Goldberg and Woodruff, 1968).

It is not likely that a hormonal secretion of a gonadal tumor be under gonadotropin control (Connor, Ganis, Levin, Migeon and Martin, 1968). In our case the hormonal studies indicate that the low basal levels of plasma FSH and LH reflect a negative feedback probably exerted by the very high basal levels of plasma testosterone. Alternatively, plasma testosterone markedly rose under dexamethasone and dropped during a combined suppression with dexamethasone and norethindrone, suggesting that the ovary bearing the tumor was responsive to progestin therapy in its hormonal secretion.

There are a few possible explanations for this finding. First, the inhibition of ACTH with dexam-
methasone might allow a higher release of LH as we have seen in a few cases (Neves-e-Castro, unpublished data). A direct stimulatory effect of dexamethasone upon the ovary does not seem to be the case, in view of previously reported opposite results (Kirschner and Bardin, 1972). Second, the addition of norethindrone and the subsequent fall in plasma testosterone concentration would again point to a role played by LH as it is well known that the secretion of the gonadotropin is inhibited by most progestational steroids.

Therefore, it is more likely to assume that gonadotropins were regulating the secretory activity of interstitial stromal cells around the tumor rather than the tumor itself (Connor et al., 1968). This assumption would implicate that the tumor does not necessarily have a hormonal secretion per se and that its hormonal effect would be indirect through the stromal reaction it includes (Jones et al., 1968; Woodruff, Goldberg and Jones, 1968). A similar explanation would be in order for other tumors like Krukenberg’s, carcinomas, etc. (Scully and Richardson, 1961). However, there is an alternative explanation for these findings based upon studies (Shane and Naftolin, 1975; Levine and Metz, 1974; Braunstein, Vaitukaitis, Carbone and Ross, 1973) that demonstrated the ectopic secretion of HCG in some tumors. The marked stromal reaction in this case might be due to a stimulation of interstitial cells by tumor secreted HCG although it would be difficult to explain again why dexamethasone or norethindrone would modulate a secretion of HCG by the tumor.

Finally, an independent testosterone secretion by the tumor cannot be excluded in view of the low basal levels of plasma FSH and LH which suggest a suppression effect by the androgen. However, we do not know of any evidence indicating that the endocrine activity of interstitial cells is independent of gonadotropin stimulation nor that it can be directly influenced by progestational 19-norsteroids.

Changes in intraovarian uptake and metabolism of LH, that markedly reduce its concentration in ovarian venous serum (Naftolin, Espeland, Tremann, Dillard and Paulsen, 1968) and/or modifications of blood flow through the ovary are new and important factors that might account for peripheral plasma LH levels (Niswender, 1975).

From the above comments it seems that in this case tumor growth was not influenced by gonadotropins in view of the sudden onset of symptomatology several years after puberty. The cause of virilism was testosterone secreted by the tumor-containing ovary, because a regression of symptoms followed unilateral oophorectomy which resulted in the normalization of plasma testosterone concentration. Although a direct proof is lacking it seems more likely that in this case the tumor acted as a chemical or mechanical ‘irritant’ to the surrounding stroma which, in turn, developed a severe hyperthecotic reaction as the source of testosterone.

We think that, on physiologic grounds, this is also what happens, but to a much lesser extent, when around a growing Graafian follicle there is a stromal differentiation into hormonally active theca cells. The polycystic ovary of Stein and Leventhal could precisely represent an intermediate stage, i.e. one lesion being the presence of many unripe unruptured follicles that would stimulate a stromal reaction expressed as hyperthecosis, and other resultant being an abnormal secretory pattern with clinical expression.

In conclusion, we postulate that many nonendocrine ovarian tumors associated with sex hormone syndromes, in the absence of ectopic HCG secretion, are due to stromal reactions with the resultant functional disorders. In addition, we think that this mechanism is also seen in the physiological development and function of thecal structures.

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