Hormonal Studies on Adrenal-Like Tumor of the Ovary—Considerations on Its Histogenesis

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A case of adrenal-like tumor of the left ovary with peripheral and ovarian venous sex steroid levels is reported. High levels of androstenedione and testosterone together with normal levels of dehydroepiandrosterone and dehydroepiandrosterone-sulfate from the left ovarian vein infer a tumor derivation from transformation of the ovarian stromal cells. (Key words: Adrenal tumor of ovary; Histogenesis) Am J Clin Pathol 1986; 86: 388-390

ADRENAL-LIKE TUMORS of the ovary are masculinizing tumors that belong to the category of lipid cell tumors. They are rare, with less than 100 cases reported in the literature. The origin of these tumors is still uncertain.

We report here the case of a woman with an adrenal-like tumor of the ovary, including a first complete study of her peripheral and ovarian venous hormonal levels, as a contribution toward specifying the histogenesis of the neoplasm.

Report of a Case

The patient, a 30-year-old woman, gravida 2 para 2, presented with a five-month history of amenorrhea. Her menarche occurred at age 12. Regular menses had occurred until two years earlier, when they became sporadic and finally stopped. During these two years, signs of masculinization developed, with some deepening of her voice and a weight gain of 60 lbs. She had no change in breast size. Surgical history included two cesarean sections and a tubal ligation.

Physical examination revealed an obese patient, weighing 276 lbs, with a height of 5 ft 7 in. and a blood pressure of 142/80 mmHg. Her skin was oily with facial hirsutism, which required occasional shaving. Balding was noted, along with increased hair growth on the back and lower abdomen and a male escutcheon over the mons pubis. Pelvic examination revealed a slightly enlarged clitoris and a normal vagina, cervix, and uterus.

No adnexal mass was seen on ultrasonography. Pertinent laboratory findings included a hemoglobin of 12.0 g/dL; hematocrit, 39.1%; plasma cortisol, 20.5 μg/dL (N: 5-25 μg/dL); serum glucose 90 mg/100 mL (N: 70-115 mg/100 mL); serum dehydroepiandrosterone (DHEA), 630 ng/dL (N: 160-700 ng/dL); serum testosterone (T), 323 ng/dL (N: 25-50 ng/dL); and a Papanicolaou smear with a maturation index of 10/90/0.

An abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. No adenexal enlargement could be palpated at surgery. Examination of the liver and other intraabdominal organs showed no abnormality. Ovarian vein blood was drawn during the procedure from the right and left ovarian veins for hormonal assessment.

Six months after the operation, the patient had lost weight to 257 lbs. Her facial and body hair were more sparse. The individual hairs were thinner, and her bald spot had filled in somewhat. The serum testosterone and androstenedione (A) had returned to normal.

Pathologic Findings

The gross appearance of the uterus was normal, and the endometrium was atrophic. The right ovary measured 3.5 X 2.8 X 2.0 cm with cystic follicles, but the left ovary measured 5 X 4 X 3 cm and was partially replaced by a 4 X 3 X 3 cm single, well-circumscribed, lobulated, rubbery, and bright yellow-orange tumor (Fig. 1).

On microscopic examination, the tumor contained two different populations of cells: large polyhedral cells with clear, granular cytoplasm and with round nuclei and nucleoli, and smaller rounded cells, with eosinophilic cytoplasm and dark nuclei. The cells appeared to be arranged in sheets, separated by a scant stroma with a rich network of vessels. No Reinke crystals were found. The cellular architecture of the tumor resembled that of the cortical zone of the adrenal gland (Fig. 2).

Specimens of blood taken from the ovarian veins at surgery were analyzed for hormonal concentrations, which were compared with the levels in the peripheral circulation (Table 1).

Discussion

A finding of an increased concentration of serum testosterone, with a normal serum DHEA and DHEA-sulfate, in a 30-year-old woman with masculinization suggests that the origin of the androgens is ovarian. This diagnosis was confirmed by the finding of an adrenal-like tumor of the left ovary at operation.

The histogenesis of this rare tumor remains a subject of controversy. Some authors think that it arises from adrenal rests, but most believe that it derives from transformation of the ovarian stromal cells, as do other lipid cells of the ovary. There is a strong possibility that both theories are true.
The left ovary is partially replaced by a 4 X 3 X 3 cm well-encapsulated adrenal-like tumor.

Two different populations of cells, large polyhedral cells with clear granular cytoplasm and smaller rounded cells with eosinophilic cytoplasm, are reminiscent of the adrenal cortex (×64).

In favor of an adrenocortical origin is the finding of frequent ectopic adrenal rests in the broad ligament in 27% of randomly selected histologic specimens and once in a fetal ovary. This contention is further supported by the return to normal of elevated urinary 17-hydroxycorticosteroid levels in some patients after surgical excision of the tumor. Adrenal cortical rests are exceptionally rare in the ovarian parenchyma, and adrenal-like tumors are almost always well encapsulated within the ovary. In 1943, Groat observed that adreno-cortical-like tissue forms in the ovarian stroma in ground squirrels after adrenalectomy.

Eveh so, most of the recent discussions of the tumor have expressed the opinion that it arises from transformation of the ovarian stromal cells. The notion of a stromal-cell origin is supported by anatomic, experimental, histologic, and endocrinologic studies.

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<tr>
<td>Testosterone (ng/dL)</td>
<td>323</td>
<td>2,400</td>
<td>350</td>
<td>10.0</td>
<td>25–50</td>
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<tr>
<td>Androstenedione (ng/dL)</td>
<td>922.2</td>
<td>13,402.0</td>
<td>1,480.0</td>
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<tr>
<td>Dehydroepiandrosterone (ng/dL)</td>
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<td>1,458</td>
<td>720</td>
<td>165</td>
<td>160–700</td>
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<tr>
<td>Dehydroepiandrosterone Sulfate (ng/mL)</td>
<td>1,930</td>
<td>2,050</td>
<td>1,950</td>
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<td>500–3,000</td>
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and in 1946 Curtis found conclusive histologic evidence of the transition between the polygonal adrenal-like cells of the tumor and the spindle-shaped cells of the normal ovarian stroma. He was the first to suggest that adrenal-like tumors of the ovary arise from the stroma cells.

Taylor and Norris, in a study of 30 lipid-cell tumors of the ovary, found adrenal-like and hilus-like cells grouped together in most instances and inferred that lipid-cell tumors probably arise from the ovarian stroma within the medulla. The stromal cells might undergo transformation to resemble both hilus cells and adrenocortical cells. Ireland and Woodruff recognized that it may occasionally be difficult to distinguish the individual adrenal-rest cells from interstitial cells.

Scully also stated that there is no way to distinguish a Leydig cell from an adrenocortical cell with certainty, so that the ovarian stroma may be the source for some lipid-cell tumors, including the adrenal-like tumors.

Kempson's ultrastructural study of an adrenal-like tumor found dark cells with irregular nuclei and dense cytoplasm similar to those found in the normal ovarian stroma. These small, dark cells have not been reported in normal adrenal tissue, so their presence suggests that the tumor originates from the ovarian stroma.

Sobrinho and Kase reported a case of adrenal-like tumor of the ovary in a 31-year-old woman with a finding of elevated testosterone levels in peripheral and ovarian vein blood. The tumor had the histologic appearance of adrenal tissue, but the patient did not have any clinical or biochemical evidence of corticosterone excess. The fact that the morphologic finding of adrenal-like tissue was not accompanied by the clinical and laboratory findings of excess adrenal activity proves against an adrenal-rest origin for this tumor. The authors concurred with Taylor and Norris that a classification of the tumor solely on the basis of morphologic appearance is artificial.

The findings from hormonal analysis in this patient, in contrast to the morphologic findings, are evidence for a stromal-cell origin for the tumor. In samples from the ovarian vein draining the tumor, concentrations of T were eightfold higher and A, 14-fold higher, than in peripheral blood. Conversely, DHEA in the ovarian vein was just twice as great, and DHEA-S was not increased at all. The high levels of A and T (principal secretions of the ovarian stroma), together with a normal DHEA and DHEA-S (principal androgens from the adrenal cortex), support the contention that adrenal-like tumors of the ovary derive from transformation of stromal cells.

It appears from our analysis, and from the observations of others, that adrenal-like tumors of the ovary arise in two different ways. Some derive from adrenal rests, although this type is rare, and the patients may have symptoms of hypercorticism in addition to masculinization. Others, the more common variety, stem from transformation of the ovarian stroma. These patients are masculinized without any signs of Cushing's syndrome.

References

5. Groat RA: Adrenocortical-like tissue in the ovaries of the adrenal-ectomized ground squirrel (citellus tridecemlineatus). Endocrinology 1943; 32:488-492