ARRHENOBLASTOMA OF THE OVARY

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Testicular tumors of the ovary were first reported by Pick (1) in 1905 and described as “adenoma tubulare testiculare ovarii.” The first report in the American literature was made by Moots (2), who described his tumor as a “fibroblastic sarcoma of embryonic testis.” The attention of the medical world was directed toward these tumors by the writings of Meyer (3, 4, 5, 6, 7, 8, 9, 10, 11), who in 1930 and 1931 reported several of them and assigned to them the now generally accepted name, arrhenoblastoma. Up to the present time there have been relatively few of these tumors recorded. Baldwin and Gafford (12) in 1936 reported a case and reviewed the literature up to that time, collecting thirty-three instances previously cited (1-34). Norris (35) in 1938 brought this bibliography up to date by adding four new cases (35, 36, 37, 38). The authors herewith present a case of arrhenoblastoma of the ovary and add to the previous lists the cases reported by Gnassi (39), Behrend and Levine (40), McLester (41), Haffner (52), Miller (53), Hitzanidès (54), and Novak (55), bringing the reported total up to 51 cases.

CASE REPORT

Mrs. M. Y., thirty-three years old, was admitted to the Presbyterian Hospital on Feb. 23, 1938, complaining of abnormal hair growth on the face and body, atrophy of the breasts, huskiness of the voice, amenorrhea, tumor in the abdomen, nervousness, headache, dizziness and weakness, all of which had become progressively more marked since August 1934. On admission to the hospital she could barely walk with the aid of two persons.

The patient had had measles, whooping cough, scarlet fever, diphtheria, and influenza in childhood and had always had a tendency to obesity. Menstruation began at eleven years of age and recurred regularly at twenty-eight-day intervals with a moderate flow, lasting four to five days. The patient had been married eleven years and had had two pregnancies which terminated spontaneously at full term. Following the birth of the second child in April 1934, she menstruated at two-week intervals until August, when the menses ceased. She was at that time twenty-nine years old. With the cessation of menstruation a gradual development of hair on the face, chin, body, and extremities was observed. There were also noticeable thickening and coarsening of the hair on the head. The hair on the arms grew to a length of about one inch, while the chin and upper lip growth became so heavy (Fig. 2) as to necessitate shaving at increasingly frequent intervals. During the past year it had been necessary to shave daily. Before the onset of her present difficulties, the patient weighed 250 pounds, but during the past three years the weight had decreased to 192 pounds and there was a change in fat distribution with a shrinking of the breasts from a large, heavy type to the flat type (Fig. 1).

1 Read before a meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., October 6 to 8, 1938. Accepted for publication in May 1940.

2 The authors wish to express their appreciation to Dr. J. L. Snively of Sterling, Illinois, who referred this patient for treatment and who provided them with preoperative and postoperative progress notes, records, and photographs.
About two years before admission to the hospital the patient suddenly lost her voice. After two weeks of speaking in a whisper it returned but with a decidedly lower pitch than previously. She had “talked like a man” since. At about the same time she noticed a swelling in the abdomen. This had become progressively larger until the time of admission, when a tumor was found filling the entire abdominal cavity. There had been increasing nervousness, headaches, loss of appetite, and frequent vomiting. During the few weeks just prior to entrance to the hospital the patient was rather acutely ill and found it difficult to get out of bed.

With the onset of amenorrhea and the development of hirsutism, there was a marked diminution in sex desire. Eventually libido was completely lost and the patient had had no sexual relations for three years.

Physical examination revealed a generalized distribution of excessive coarse hair on the face, particularly on the chin and upper lip, the arms, the chest, the abdomen, and the legs. The pubic hair was very long and coarse and presented an escutcheon similar to that of the male (Fig. 1). The voice was coarse and had male qualities. There was an acne over the face and upper chest. The breasts were atrophic and contained no palpable glandular tissue. The labia majora were atrophic, as in a postmenopausal patient, while the clitoris was elongated to about three times the normal size. There was a mass filling the abdomen to the xiphoid process. Bimanual palpation revealed that this tumor arose from the pelvis and had pushed the uterus to the left. The uterus itself was small and atrophic. The eye grounds were negative.

A blood count showed erythrocytes 3,450,000, hemoglobin 65 per cent (Dare), and leukocytes 12,400. Blood pressure was 110/80; the urine was negative for albumin and sugar; the basal metabolic rate was plus 23 per cent. A Friedman modification of the Aschheim-Zondek test was negative.

Operation was performed on Feb. 29, 1938. A cystic mass was found which filled the abdomen. Manual exploration revealed a few omental adhesions on the left side and showed that the mass originated in the right ovary. Aspiration of 2000 c.c. of bloody fluid, made it possible to lift the tumor through the abdominal incision. The pedicle of the ovary was clamped across and the tumor removed. The left ovary was thin, elongated, and sclerotic, resembling closely the normal postmenopausal ovary. The uterus was small and in good position.
The patient had an uneventful convalescence, leaving the hospital on the eleventh postoperative day.

The subsequent history we quote from a report sent us by Drs. J. L. and R. Snavely on July 5, 1938:

"Mrs. Y.'s first menstrual period was that of March 27th. It persisted seven days. The flow was moderate in amount, and was accompanied by a few cramps on the first day only, these being very mild in comparison to those she regularly suffered before tumor symptoms appeared. No clots were passed.

"The second period began on April 20 and was about the same, except that there were no cramps.

"The third period occurred on May 11 and lasted one day only. Severe cramps occurred in the afternoon, followed by the passage of a clot about the size of an egg. A rather severe sacral backache was noticed for two days after the clot was passed.

"The fourth period began about June 9. The patient states that a profuse flow suddenly appeared, with no premonitory signs whatever. As she described it, the flow was so sudden and so profuse that before she knew what was happening it had stained her clothing extensively. This period lasted ten days. No cramps or clots were noted. After this period the patient felt apathetic and a bit weak, though not enough to hinder her in her work.

"The fifth period began on June 27 and bids fair to resemble the fourth in mode of onset and quantity.

"General symptomatic check-up shows:

"1. Breast development: She now wears a size 42 brassiere, which is the size she used before the tumor developed as compared with the 40 she needed just before operation.

"2. General condition: She says that she now feels better than ever before in her life. Her appetite is excellent and she has a bowel movement daily without enemas or other aids.

"3. Urinary: No symptoms; the nocturia which she had before operation has disappeared.

"4. Weight: Now 191 pounds. The patient thinks she weighed only 160 pounds when she left the hospital."
Hair: There is still some hair on the chest, though not as much as before the operation. There is also some hair on the forearms, but this is definitely softer and lighter than before. She still shaves but finds it necessary to do so only every fourteen days. At present she can shave two or three times with the same blade; before operation the blade was dulled by one shaving. The appended picture (Fig. 3) was taken eleven days after shaving. In this time she has grown about the equivalent of a two-day male growth.

Sex Relations: Before operation she derived no satisfaction whatever from intercourse; in fact, the idea was revolting to her. At present, however, she states that she enjoys it as much as she did the first year she was married. No contraceptives are used.

Muscles: Mrs. Y. tells me that her muscles are definitely softer than they were before operation, when they were hard and knotty.

Extensive chemical and hormonal studies were planned in order to aid us in our diagnosis. The results of chemical studies on the urine and blood, carried out by Dr. M. Freeland, biologic chemist at the Presbyterian Hospital, are shown in Tables I and II.

**Table I: Urinary Chemical Studies**

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<tr>
<th>Date</th>
<th>NaCl</th>
<th>Creatinine</th>
<th>Creatine</th>
<th>Sodium</th>
<th>Potassium</th>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feb. 28</td>
<td>4.08</td>
<td>0.633</td>
<td>0.070</td>
<td>1.303</td>
<td>0.430</td>
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<tr>
<td>Mar. 10</td>
<td>3.725</td>
<td>0.213</td>
<td>0.079</td>
<td>1.697</td>
<td>0.513</td>
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<tr>
<td>Apr. 20</td>
<td>8.288</td>
<td>1.181</td>
<td>0.057</td>
<td>6.336</td>
<td>1.659</td>
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<tr>
<td>Aug. 13</td>
<td>16.6</td>
<td>0.97</td>
<td>0.05</td>
<td>6.78</td>
<td>1.135</td>
</tr>
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<td>Variable</td>
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<td>None</td>
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<td>2 to 3</td>
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**Table II: Blood Chemical Studies**

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<th>Date</th>
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<th>Creatinine</th>
<th>Creatine</th>
<th>NaCl</th>
<th>Sodium</th>
<th>Potassium</th>
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<td></td>
<td></td>
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<tr>
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<td>8.3</td>
<td>24.0</td>
<td>1.4</td>
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<tr>
<td>Mar. 10</td>
<td>12.8</td>
<td>29.3</td>
<td>1.1</td>
<td>2.78</td>
<td>505</td>
<td>208.2</td>
<td>29.2</td>
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<tr>
<td>Apr. 20</td>
<td>12.4</td>
<td>26.0</td>
<td>1.5</td>
<td>3.36</td>
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<tr>
<td>Aug. 13</td>
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<td>15 to 25</td>
<td>1.6</td>
<td>2 to 6</td>
<td>450-550</td>
<td>300 to 330</td>
<td>11 to 20</td>
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</table>

The calculations for Feb. 28 were made after extraction from a 68.5 hour urine totaling 3740 c.c.; the March 10th figures were derived from a 96-hour urine with a total volume of 2790 c.c.; the April 20th studies were made upon a 48-hour urine with a total volume of 3340 c.c., and the August 13th determinations were on a 48-hour urine of a total volume of 3540 c.c. All values are expressed in terms of grams per twenty-four hours. The blood studies are expressed in terms of milligrams per 100 c.c.

Hormonal studies on the urine and on a part of the tumor were conducted by Dr. F. C. Koch of the Department of Biochemistry of the University of Chicago. Extractions with assay were carried out according to the methods of Gallagher and Koch, and revealed the following values:

- Feb. 28, 1938: Pre-operative urine, 51 capon units in 24 hours.
- March 10, 1938: 1 week postoperative urine, 5 capon units in 24 hours.
- April 20, 1938: 2 months postoperative urine, 15 capon units in 24 hours.
- Tumor tissue, 175 grams: less than 1 capon unit total.

Pathology: The specimen consists of a large ovarian tumor, 28.5 X 23 X 11 cm., weighing 4640 grams after the removal of 5000 c.c. of blood-stained fluid. The external surface is smooth with no vegetations, but with numerous small cystic masses protruding. The wall is of variable thickness, measuring up to 8 cm. in some places. The interior is made up of a rather dense tissue. There are numerous small and large cavities lined by firm tissue and a great mass of necrotic material through the entire tumor, this material varying in color from a dirty gray to a dark red, which resembles old blood clot.
Microscopic Examination (Dr. Walter Schiller): In the undifferentiated fibrous stroma there is a small island of loose connective tissue poor in nuclei. Imbedded in this is a wedge-shaped island containing canaliculi of various diameters running parallel to the axis of the wedge. These canaliculi in some instances have short blunt ends, while in other places they anastomose in antler-shaped formations. The canaliculi are lined by low cuboidal epithelium with large dark nuclei. This structure corresponds to an incompletely developed embryonic rete (Fig. 4). To the right are trabeculae of firm fibrous connective
tissue, imbedded in which are small canaliculi partly straight, partly curved, running in various directions. These are lined by high columnar epithelium with pale translucent protoplasm and nuclei at the base. In the stroma adjacent to the canaliculi are scattered a few large polyhedral cells with dark reddish protoplasm, the spermatic ducts close to the rete (Fig. 5).

Fig. 6 shows the dense stroma of the tumor. In the center the interstitial tissue forms a homogeneous ground mass in which are found round and oval cells of lighter translucent protoplasm with pale vesicular nuclei. The fat stains show round fat droplets in the protoplasm. Surrounding these cells is a darker staining fibrous capsule. This tissue is young, partially developed cartilage. This part of the tumor is mesenchymatous, teratomatous tissue.
Loose connective tissue containing short parallel small trabeculae, partly branching, is shown in Fig. 7. These consist of one to three layers of low columnar epithelium with large dark nuclei. These trabeculae undergo transition into canaliculi by forming a small narrow lumen in some parts (outside the field). Adjacent to these canaliculi small clusters of large polyhedral cells with comparatively small pale nuclei and dark red staining protoplasm are seen (interstitial cells of Leydig). This part of the tumor corresponds to embryonic male genital cords with large spermatogonia, representing typical arrhenoblastoma tissue.

Numerous small and large cystic cavities were present, lined by high columnar epithelium with pale protoplasm and oval nuclei perpendicular to the basement membrane. The larger cyst cavities have the epithelium flattened out and partly cast off. These cystic portions of the teratomatous tissue are illustrated by Fig. 8.

DISCUSSION

The arrhenoblastoma is an ovarian tumor, usually unilateral and in most instances benign, which may produce a definite symptom-complex and has typical microscopic characteristics. The clinical picture is that of defeminization and masculinization, a condition that reverts toward the normal following removal of the tumor.

The chief symptoms, as described by Schiller (42), are hirsutism, with the development of a chin and upper lip beard, masculine pubic escutcheon, and the growth of coarse hair on the chest and extremities; hypertrophy of the clitoris; hypertrophic laryngitis with the acquisition of a deeper and more resonant voice; amenorrhea. Associated with these are atrophy of the breasts, redistribution of fat, broadening of the shoulders, an increased firmness of the skeletal musculature, changes in facial contour with apparent heightening of the cheek bones, acne of the face and chest, and loss of libido.

Histopathologically we may find other types of ovarian tumor in association with arrhenoblastoma, viz., the teratomatous structure here seen and the pseudomucinous tumor of Haffner (52). In general, there are three types of arrhenoblastoma which may be found alone or intermixed as in this case. The
first type is that described by Pick (adenoma tubulare testiculare ovarii), in which there are areas containing cuboidal epithelial cells arranged in tubules in a manner that produces a facsimile of the testicle. The second type contains cells of the same type in solid blocks and masses, with an arrangement that tends to produce cords but not tubules. The third type is that in which the solid areas are produced by a grouping of undifferentiated spindle-shaped cells in eccentric arrangement resembling sarcoma (fibroblastic sarcoma of embryonic testis, Moots).

As to blood and urinary chemical values in association with the presence of an arrhenoblastoma, before operation we have relatively normal readings for the blood urea nitrogen, total non-protein nitrogen, creatinine, creatine, and sodium chloride. The urinary creatinine is low and the creatine is high. The blood serum sodium is markedly decreased, while the potassium is increased. Both the sodium and potassium in the urine are decreased. The increase in serum potassium with the decrease of this element in the urine can be explained by a natural process of retention with restrained output. The decrease of sodium in both blood serum and urine is difficult to explain. All values here reported showed a definite trend toward normal after operation. This makes us feel that the variations from the generally accepted normal found before removal of the tumor were unquestionably based upon the presence of the arrhenoblastoma.

Most authorities agree that the site of production of the male sex hormone is in the interstitial cells of Leydig. A study should show the presence of these cells in tumors that have produced the clinical picture of defeminization and masculinization. The Leydig cells are capable of producing large amounts of sex hormone, so that relatively few of them in a tumor can obtain mastery over the ovarian function. The amount of defeminization and masculinization in any given case depends directly upon the activity of the existing Leydig cells. Because of this, no matter how highly specialized the tumor may be microscopically, the clinical symptoms produced are directly proportional to the number and activity of the male-hormone-producing cells. A small amount of this hormone may produce no clinical change, a somewhat greater amount may result in defeminization but not masculinization, while a large amount of circulating male hormone produces the full picture as seen in this case.

Male sex hormone determinations on the urine revealed what, according to Kenyon and his co-workers (44), may be considered as a normal output. Koch (43) found that males and females eliminated about equal amounts of male sex hormone in the urine. Wolf (45) states that a normal excretion is 6 to 10 capon units per liter. If this be true, the preoperative urine with a twenty-four-hour assay of 51 capon units in 3740 c.c. is high, but the work of Kenyon and his associates is more recent. In their report, sixteen women with virilism of types other than arrhenoblastoma (adrenal, pituitary and unclassified) had an average twenty-four-hour output of 26 capon units. But the authors go on to state that they allow 40 per cent for destruction in the process of extraction, so that they consider 28 to 77 capon units as normal output. This being the case, we must conclude that in the presence of an arrhenoblastoma the excretion of urinary male sex hormone is little if any increased.
Estrogenic hormone determinations are being made, but at the present time are not complete.

Differential Diagnosis: When virilism exists in the female, several conditions must be considered in the differential diagnosis. The adrenal gland and the pituitary are both capable of producing conditions which resemble the clinical picture which may result from arrhenoblastoma. Classically we must consider tumors of the androgenic portions of the adrenal gland and the basophilic adenoma of the pituitary gland (Cushing, 49). Grollman (46) states that tumors of the adrenal cortex proper do not produce virilism, or what he calls the adrenogenital syndrome, this function being a product of tumors in the androgenic zone.

Cushing's syndrome, basophilic adenoma of the pituitary gland, is characterized by hypertrichosis and amenorrhea, without hypertrophy of the clitoris or larynx. There are hypertension, glycosuria, obesity about the face, neck, and trunk, acrocyanosis, purplish striae on the thighs, and interference with the fields of vision. Pelvic examination reveals no ovarian tumor. Diabetes of bearded women as described by Achard and Thiers (50), is now considered to be the same as Cushing's syndrome.

The adrenogenital syndrome is somewhat more difficult to differentiate from arrhenoblastoma. Here we have all the salient clinical features of both conditions paralleling each other. Amenorrhea, hypertrophy of the clitoris, laryngeal enlargement, and hirsutism, together with breast atrophy, changes in fat distribution, and loss of libido, are common to these two masculinizing influences. The differentiation must be made on several points. Bimanual pelvic palpation revealing an ovarian tumor would lead to a diagnosis of arrhenoblastoma, but the tumor may be so small as to elude the most careful examining fingers. In such a case, we must resort to adrenal visualization by perirenal air insufflation, and even then we may be dealing with a minute adrenal tumor which cannot be visualized. Hormonal studies, at the present time, are of no apparent help. The only factors that might give us a clue as to the precise diagnosis would be a careful blood and urinary chemical study. In the presence of adrenal tumors there is hypertension associated with a decrease in the serum sodium and an increase in the serum potassium. The urinary sodium is increased to three times normal and the potassium is decreased (51). The differences between these values and the ones found in the case reported here are striking (Tables I and II). Also present in the adrenogenital syndrome and not in arrhenoblastoma are increases in the nitrogenous product retention to five or six times the normal value.

Summary and Conclusions

1. A case of arrhenoblastoma of the ovary with teratoma in a white woman thirty-two years of age is reported.
2. This is the fifty-first case to be reported in the literature.
3. Hormonal studies of the urine revealed a high normal or slightly increased male sex hormone urinary output.
4. Chemical studies show decreased serum sodium and increased serum potassium with relatively normal urea, non-protein nitrogen, and creatinine. Urinary chemical studies show both sodium and potassium to be decreased.
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5. Differential diagnosis between arrhenoblastoma of the ovary, basophilic adenoma of the pituitary gland, and the adrenogenital syndrome is discussed.

BIBLIOGRAPHY