GRANULOSA-CELL TUMORS OF THE OVARY

WITH REPORT OF A CASE

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As its name indicates, the so-called granulosa-cell tumor is believed to be related histogenetically to the granulosa cells of the graafian follicle. The relationship, however, is probably not a direct one in the sense that the tumor cells are descendants of granulosa cells of adult follicles. The view held by Meyer (28), which is the one most generally accepted at the present time, is that these tumors originate from granulosa-cell rests left over in the embryological development of the ovary. Robinson, however, has recently brought forward evidence in favor of the older view, that the tumors originate from graafian follicles. The relationship of the tumor cells to granulosa cells seems evident both from morphological and physiological considerations. Morphologically the tumor cells resemble normal granulosa cells of the graafian follicle and they are often arranged in formations suggesting a primordial follicle or an adult follicle. From the physiological standpoint, it appears to be definitely established that the tumor produces the follicular ovarian hormone.

Von Kahlden is commonly credited with being the first to describe a case of granulosa-cell tumor of the ovary, in 1895, under the name of “a peculiar form of ovarian carcinoma.” He claimed that no case similar to his had previously been reported. Robinson, however, says that Rokitansky in 1855 described a type of ovarian carcinoma composed of epithelium closely resembling the granulosa of the follicles and containing folliculoid and ovuloid bodies. In 1890 Acconci described structures similar to primordial ova in a papillary cystoma of the ovary. He interpreted these structures as products of a neoplastic process, and not as ova remaining in an ovary the seat of cystic degeneration, as Rokitansky and others had done.

Von Kahlden’s report deals with the structure of the tumor, but gives no information in regard to the clinical aspects of the case except that the tumor was removed at operation from an eighteen-year-old girl. He described a carcinomatous portion of the tumor similar to a so-called cylindroma, and an adenomatous portion containing follicle-like formations. The smallest and simplest of these formations were about the size of a primordial follicle, and were similar to the latter in structure, consisting of a row of cubical epithelium surrounding a protoplasmic disc staining dark red with eosin. In the center of the
smallest of these follicle-like formations was an oval nucleus staining paler than the nuclei of the marginal cells, the whole structure recalling a follicle containing an ovum. In the larger follicle-like formations the central protoplasmic disc contained several nuclei.

Following von Kahlden's report there appeared at infrequent intervals reports of similar cases under various names. Schröder (42) in 1901 described an ovarian tumor removed at operation from a woman thirty-six years old. He believed that the new formation arose from follicle epithelium, and that the follicle-like structures and their contents represented an attempted new formation of follicles and ova. He emphasized, however, that the contents of the follicle-like structures were completely different from ova, although the structures themselves closely resembled true follicles. Schröder proposed the name "folliculum" for this tumor, which he thought belonged with the "adenocarcinoma folliculare" of von Mengershausen, the "adenoma folliculi Graafiani" of von Kahlden, and the "folliculoma malignum ovarii" of Gottschalk. Liepmann, in 1904, in a paper dealing with ovum formation in carcinoma of the ovary, came to the conclusion that the ovum-like structures which had been described in these tumors were not true ova, but products of a regressive metamorphosis. This view seems to be generally held at the present time.

Brenner, in 1907, reported three cases of "oophoroma folliculare" and emphasized that the follicular structures of the tumors were very similar to normal ovarian follicles. Werdt, in 1914, reported six cases of ovarian tumor in which the epithelium was similar to the epithelium of the primordial follicle and of the membrana granulosa, as well as of the granulosa strands described by Walthard. The formation of follicle-like cysts with membrana granulosa and theca externa was striking. The theca interna and the ovum were missing. These characteristics led Werdt to assign the origin of the tumors to the germ epithelium, especially to the Walthard granulosa cells, and to combine them in a group as granulosa-cell tumors.

Meyer (24), in 1915, reported twelve cases of ovarian tumor under the name of "carcinoma ovarii folliculoides et cylindromatosum." Only a few of these were of the folliculoid type described by von Kahlden, the remainder showing mainly a cylindromatous or other type of structure, often with transitions to the folliculoid type. Meyer suggested, as an explanation for the different histological pictures observed, an origin from rests of epithelial cells left behind at various stages of development of the follicles, the histological character of the resulting tumor depending on the degree of differentiation of these hypothetical rests. He regarded the contents of the small follicle-like structures as a secretion of epithelial origin which is increased through epithelial destruction. In 1918, in a discussion of folliculoid and cylindromatous ovarian carcinoma, Meyer (25) said that he did not regard the ripe follicle epithelium as a source of origin of the tumor growth because he had never observed growth of any kind in it and because it is dependent for its existence on the ovum. A further point advanced by Meyer (28)
against an origin from follicle epithelium is the frequent occurrence of the tumor in women long past the menopause, in whom the ovary no longer contains follicles.

Granulosa-cell tumors usually involve the ovary to such an extent that it is impossible to determine whether the point of origin is in the cortex or in the medulla. Because of the occurrence of granulosa-cell rests in the medullary portion of the ovaries of every full term fetus, it might be assumed that in adults, also, the rests would be situated chiefly in the medulla (Meyer, 28), and in a few instances this has been found to be the case. Meyer (28) observed two such instances, one in a woman of forty-five years and the other in a woman of forty. In the ovary of the woman forty years old the granulosa cells of the medulla showed evidence of proliferation, the appearance suggesting small tumors. The patient was otherwise normal. TeLinde described a granulosa-cell tumor 3 mm. in diameter situated in the medulla of the ovary in a woman forty-three years old. He believed that this situation practically excluded an adult follicle as the origin, and that practically the only possible source in this case would be embryonal rests of ovarian parenchyma closely related to granulosa epithelium left in the medulla in embryonic life.

Robinson, in 1930, took issue with the proponents of the theory that granulosa-cell tumors originate from embryonic rests. In the ovarian parenchyma not replaced by tumor growth he found follicles showing marked proliferation of their granulosa, which extended outward into the stroma. Some of the follicles were moderately cystic and some contained ova. He claimed that the round or oval spaces present in these tumors, even when devoid of normal or recognizable intrafollicular contents, are the remains of real follicles. His conclusion is that granulosa-cell tumors originate from the epithelium of ovarian follicles, and that the different types that have been described represent different phases of growth of one and the same tumor. Ewing (10) says that an origin of folliculoma malignum from undeveloped follicles is indicated by a diffuse neoplastic overgrowth of the lining cells of the small cortical follicles. Schröder (42) observed in a case of granulosa-cell tumor a proliferation of the follicle epithelium in the opposite ovary which he regarded as a beginning stage of granulosa-cell tumor formation.

Recently much attention has been paid to the hormonal effects produced by granulosa-cell tumors. Schröder (43), in 1922, presented a case of granulosa-cell tumor of the ovary associated with glandular-cystic hyperplasia and beginning carcinoma of the endometrium in a woman forty-five years old, who had had metrorrhagia for four months. He believed that the tumor exerted an action analogous with that of the ripe, abnormally persisting follicle which in the last part of the child-bearing period produces a pathological proliferation in the endometrium. On the basis of the greatly hyperplastic endometrium the tendency to carcinoma had developed. Neumann (32) in 1924 reported a similar case except that there was no carcinomatous change in the
hyperplastic endometrium. The patient had had metrorrhagia for ten years, alternating with periods of amenorrhea. He attributed the functional and anatomical changes of the endometrium to a functional anomaly of the ovary.

In 1925 Meyer (26) reported on hypertrophy of the uterus, and especially the endometrium, in seven cases of ovarian tumor in women beyond the menopause. Four of the tumors were diagnosed as folliculoma ovarii, two as sarcoma, and one as fibroma. He assumed that a specific stimulus from the tumors was responsible for the uterine changes and raised the question as to whether granulosa-cell tumors can transform themselves into fibroma and sarcoma by gradual loss of their epithelial parenchyma. In this connection, Novak and Long say that the occurrence of a sarcomatous structure in granulosa-cell tumors is not surprising in view of Fischel's work on the embryology of the ovary, which indicates that the granulosa is of mesenchymal origin. In 1931 Meyer (28) reported thirty-three cases of granulosa-cell tumor, and emphasized the accompanying uterine changes and the history of irregular bleeding. Habbe the same year reported the same group of cases in greater detail. Bleeding was an important symptom in twenty-seven cases, and hyperplasia of the endometrium was present in all cases in which the endometrium was examined (nineteen). After removal of the tumor, abnormal bleeding stopped, and in younger women menstruation became normal. In four women in the climacterium bleeding was absent in spite of endometrial hyperplasia. In two cases hypertrophic breasts were found, and in two old women there was galactorrhea. Two children, five and eleven years of age, showed precocious development, uterine bleeding, hypertrophic breasts, and one of the two even colostrum secretion. Klaften (17), Fauvet, Novak and Long, TeLinde, Schulze, and other recent writers have described uterine enlargement, hyperplasia of the endometrium, and irregular uterine bleeding in association with granulosa-cell tumors.

Post-climacteric bleeding in other types of ovarian tumor is infrequent. TeLinde found bleeding in only nine of forty-one cases of ovarian tumor in the post-climacteric period. In three or more of these there was extension of ovarian carcinoma to the uterus. In none were there recurring periods of profuse bleeding. Moulonguet-Doléris found metrorrhagia in about 25 per cent of seventy-four cases of ovarian tumor in women past the menopause. Fauvet, from a study of forty-six ovarian carcinomas occurring after the menopause, concluded that glandular-cystic hyperplasia of the endometrium as a cause for uterine bleeding in ovarian tumors comes in question only in the presence of granulosa-cell tumors.

Hyperplasia of the endometrium in cases of granulosa-cell tumor may be accompanied by adenomyoma of the uterus, as noted by Tietze, King, Klaften (16), and TeLinde, or by adenocarcinoma, as noted by Schröder (43) and TeLinde. Szathmáry in his review of granulosa-cell tumors found adenocarcinoma associated with hyperplasia of the endometrium in four cases, and adenomyosis interna in eight cases.
Blau, Rummel, Pahl, Novak, and Klaften (18) reported cases of granulosa-cell tumor in children three to nine years of age. Vaginal bleeding was present in all of these cases, and most of the patients showed enlarged breasts, axillary and pubic hair, and a body contour tending toward the mature type. Some gave a history of rapid growth and of psychic changes toward the mature type. In Klaften’s case in a nine-year-old girl, the voice changed from that of a child toward the adult type. Hypertrophy of the uterus was observed at operation in this case and also in one of Novak’s patients, a child six years old. Removal of the tumor in these cases in children was followed by cessation of bleeding, and by a regression, or a tendency toward regression, of the abnormal secondary sex characteristics. The bleeding in children and in women past the menopause may show a tendency toward periodicity, which, according to Novak, may be due to fluctuations in the folliculin level.

In addition to the uterine bleeding in cases of granulosa-cell tumor, there may be periods of amenorrhea. Aschner reported a case in a woman of twenty-five from whom a granulosa-cell tumor was removed and who gave a history of long periods of amenorrhea alternating with periods of prolonged excessive bleeding. Klaften (17) reported that in four cases of granulosa-cell tumor in women in the child-bearing age, there was a history of long bleeding and amenorrhea. In all four of these cases, and in Aschner’s case, menstruation became normal after removal of the tumor. According to Habbe, complete histories in cases of granulosa-cell tumor show that the amenorrheic phases are usually followed by bleeding. Lepper, Baker, and Vaux noted that in their cases of granulosa-cell tumor in younger women there was a history of amenorrhea followed by bleeding, and Szathmáry, reviewing forty-two collected cases in women of child-bearing age, found temporary amenorrhea in nineteen or 45 per cent.

Klaften (17) found corpus luteum-like and corpus albicans-like elements in many granulosa-cell tumors. He also claimed that he was able to demonstrate functional stages in the glands of the endometrium in three cases of granulosa-cell tumor in women in the climacterium. He believes that the periods of amenorrhea which occur in so many cases of granulosa-cell tumor, as well as the functional stages of the endometrium in women in the climacterium who are carriers of granulosa-cell tumor, are explainable by the presence of the corpus luteum-like structures in the tumors. In the tumor removed from Aschner’s patient, a woman of twenty-five, with a history of long periods of amenorrhea alternating with periods of bleeding, a corpus luteum-like area was present. Plate reported a granulosa-cell tumor of a rare type, the lipoid folliculoma of Lecène, in a twenty-three-year-old patient who gave a history of metrorrhagia alternating with amenorrhea. At the time of operation, amenorrhea had existed seven months, the breasts were swollen, and colostrum could be expressed. The tumor cells contained much lipoid material, but there were transitions to the typical picture of folliculoid granulosa-cell tumor in some areas. In a few
cases of granulosa-cell tumor in women past the menopause the uterus has been found to be greatly enlarged and the endometrium transformed into a decidua-like structure. Dworzak reported one such case in a woman fifty-two years old, and Leibbach reported another in a woman sixty years old. Arnold, Koerner, and Mathias reported a similar case in a woman sixty-three years old, although the ovarian tumor in their case was diagnosed as medullary and glandular carcinoma and not as granulosa-cell tumor.

**Hormone Studies**

The enlargement of the uterus, the endometrial hyperplasia, and the uterine bleeding, especially when occurring in young children and in women past the menopause; the functional stages of the endometrium in women in the post-climacteric period, including stages of decidua formation; and the rapid growth and the appearance of secondary sexual characteristics in young children, all speak for a hormone action in cases of granulosa-cell tumor. This clinical evidence has been supplemented in a few instances by hormone studies on experimental animals.

Schuschania made quantitative estimations of folliculin in a case of a granulosa-cell tumor in a woman nine years past the menopause. In a five-day period before operation there was an excretion of 326 mouse units in the urine, and 619 mouse units in the feces. In the eight days following operation there was an excretion of 158 mouse units in the urine. Sixty-six days after the operation there was no folliculin demonstrable in either urine or feces. Frank tests on 40 c.c. of venous blood obtained on the day of the operation, and on 5 c.c. of blood taken from a vessel in the capsule of the tumor during the operation, were positive. Meyer (27) obtained a positive estrus reaction in castrated mice with an extract prepared from a granulosa-cell tumor from a thirty-six-year-old woman. Frank found female sex hormone in an extract prepared from an ovarian tumor from a child showing premature sexual development. This tumor was later diagnosed as granulosa-cell tumor by Novak and Meyer. In two other cases of ovarian tumor in children showing premature sexual development Frank found female sex hormone in the urine for one week postoperatively. These two tumors were diagnosed as malignant teratoma and medullary carcinoma. Neumann (33), in a case of granulosa-cell tumor in a woman forty-six years old, was able to demonstrate the presence of folliculin in 40 c.c. and in 20 c.c. of blood before the operation, while six weeks after the operation none could be demonstrated in 80 c.c. In another case in a woman sixty-one years old he demonstrated folliculin in 60 c.c. of blood before the operation. With a piece of the tumor, as well as with an extract of the tumor, he obtained a positive estrus reaction in castrated mice. Eighteen weeks after the operation no follicle hormone could be demonstrated in 60 c.c. of blood. Pahl injected urine from a nine-year-old girl with a granulosa-cell tumor, into four infantile mice, and in one of the four corpora lutea and follicle bleeding occurred.
Later tests were negative. The tumor showed no lutein elements. Daily reported a weakly positive Aschheim-Zondek reaction in a case of granulosa-cell tumor in a woman twenty-seven years old who had had amenorrhea for sixteen months. Schulze performed Aschheim-Zondek tests on two of her cases and obtained negative results.

**Frequency**

Granulosa-cell tumor of the ovary is relatively rare. Meyer's (28) group of 33 cases and Novak and Long's group of 26 cases constitute the largest single collections. The frequency of occurrence in relation to ovarian carcinoma as a whole is given in three reports as follows: 14 cases in a group of 172 carcinomas (Klaften, 18); 8 cases in a group of 76 carcinomas (Fauvet); 4 cases in a group of 43 carcinomas (Schulze). According to these reports, granulosa-cell tumors constitute from 8 to 10 per cent of all ovarian carcinomas. Szathmáry found 9 granulosa-cell tumors among 203 malignant ovarian neoplasms (4.4 per cent). This author in 1933 reviewed 126 cases of granulosa-cell tumor, including his own 9 cases, 32 cases of Meyer, and 85 cases in the literature. Cases in the American literature are rare. With the exception of the 26 cases collected at the Johns Hopkins Hospital and reported on by Novak and Long, and earlier in part by TeLinde, there are apparently only 17 cases, reported as follows: 7 by Schulze, 4 by Robinson, 2 by Wolfe and Kaminester, 2 by Daily, 1 by Taussig, and 1 by Eiss.

**Age Incidence**

Meyer (28) found granulosa-cell tumor most frequently in women sixty to seventy-four years of age. Szathmáry, reviewing 120 cases in which the age was given, found that over half occurred in women over fifty years of age, and that forty-two occurred in the child-bearing age. Seven cases have been reported in children three to nine years of age (Blau, Rummeld, Pahl, Novak, and Klaften, 18).

**Gross Characteristics**

According to Novak and Long, the size of granulosa-cell tumors varies in general from that of a hickory nut to a grapefruit. One of TeLinde's tumors measured 3 mm. in diameter, while another measured 30 cm. and weighed 20½ pounds. The tumor surface is usually smooth and often somewhat lobulated. Adhesions between the tumor and neighboring structures are uncommon. The tumors may be predominantly solid or predominantly cystic, with all gradations between these extremes. Even the practically solid tumors usually show a few small cysts. The cysts vary all the way from those just within the range of visibility to those many centimeters in diameter. The consistency of the tumor varies according to the prevalence of cysts and the extent to which degeneration has taken place.
The tumor tissue may be pale yellow or grayish, although interstitial hemorrhage or degenerative changes may give rise to dark red or yellowish, soft, gelatinous or cystic areas. The tissue is usually soft and friable, and sometimes granular. According to most descriptions, vascularity is pronounced, and the whole tumor sometimes has a bluish appearance. One case is described by Taussig in which there was a large amount of blood found free in the abdominal cavity at operation, coming from a ruptured granulosa-cell tumor. Klaften (18) also described a case in a nine-year-old girl in which the tumor was found ruptured with free blood in the abdominal cavity. Usually the tumors are enclosed by a definite thin, fibrous capsule. The cysts are filled with a yellowish, turbid, watery fluid. The fluid may, however, contain blood or products of tumor degeneration.

Of 80 cases of granulosa-cell tumor collected by Klaften (17), the tumor was bilateral in 5 or 6.2 per cent. Of 126 cases reviewed by Szathmáry, in 101 the site of origin was given as follows: right 47, left 44, bilateral 10 (about 10 per cent). Of these 126 cases, 123 were operated upon. In only 17 were adhesions found, and in only 6 was there difficulty in removing the cancer-like degenerated portions of the tumor. Ascites was mentioned 12 times. Of the 126 cases, 120 were accurately described, and of these, 68 were predominantly cystic and 52 predominantly solid. Klaften (17) frequently found straw-yellow areas in his tumors which microscopically showed a corpus luteum-like structure.

MICROSCOPIC CHARACTERISTICS

The histologic picture presented by granulosa-cell tumors shows considerable variation in different tumors and in different parts of the same tumor. The commonly recognized types are the folliculoid, the cylindromatous, and the mixed. Tumors of pure folliculoid type are the least common, while those of predominantly cylindromatous structure, with more or less folliculoid areas here and there, are the most common. Tumors of atypical structure having a sarcomatous appearance are also included with the granulosa-cell tumors if they show transitions to the familiar folliculoid or cylindromatous patterns, and especially if, in addition, they show evidence of follicular hormone production. Habbe divided 33 cases as follows: 4 folliculoid, 5 cylindromatous, 24 mixed (cylindromatous and folliculoid, and diffuse cases difficult to recognize).

In the folliculoid form the tumor cells tend to form structures resembling graafian follicles. The smallest of these structures are about the size of a primordial follicle and they are lined by a single row of cuboidal epithelium. The larger folliculoid structures consist of a zone of granulosa-like cells, several or many cell layers in thickness, enclosing a cavity. The cells of the inner and outer rows tend to be cuboidal or columnar and are arranged radially. The cells between the inner and outer rows are polygonal and closely packed. The tumor cells are rather uniform in size and staining qualities. Mitotic figures are usu-
ally scarce or absent. The cell nuclei are round or oval, somewhat vesicular, and stain dark blue with hematoxylin. The cytoplasm is scanty, and stains lightly with eosin. The follicle-like structures contain in their enclosed cavities an eosin-staining colloid-like homogeneous substance and sometimes cells in various stages of disintegration. The smaller folliculoid structures may contain in the center a single large pale cell, giving an appearance somewhat resembling an ovum in a follicle. Habbe suggests that there may be a secretion poured into the follicle-like structures and that a few cells may be cast off with the secretion, as occurs in the case of other secretions. Meyer (24) and Wolfe and Kaminester regard the cyst contents as a secretion. At the periphery of the follicle-like structures there is frequently a hyalinized basement membrane, and rarely a zone of epithelioid cells similar to theca interna (Meyer, 25). Many of the larger cysts in granulosa-cell tumors are probably the result of degenerative processes. Other cysts of considerable size are lined by a definite border of granulosa-like cells, and in this border there may be small follicle-like structures which have been compared with the Call-Exner bodies of the graafian follicle of a rabbit. The stroma in granulosa-cell tumors is fibrous in nature, and the degree of cellularity varies. Immediately around the folliculoid structures the cells may be numerous and have a concentric arrangement suggesting theca externa. There may be relatively acellular wavy hyalinized areas which have been likened to corpora albicantia by Aschner, Schulze, and others.

In the cylindromatous type of growth the tumor cells are arranged in solid cords or strands which may be markedly convoluted, giving a characteristic picture often described as a moiré silk pattern. The tumor cells are similar to those of the folliculoid form, although they are less uniform in structure and bear less resemblance to normal granulosa cells. The stroma separating the solid strands of tumor cells is fibrous and sometimes hyalinized. In typical cylindromatous areas there is relatively little stroma. Very often there can be found somewhere in a cylindromatous granulosa-cell tumor small or large follicle-like structures, as above described.

The atypical sarcoma-like granulosa-cell tumors present a bizarre histological appearance. From the morphological standpoint, a diagnosis is possible only when transitions toward the folliculoid and cylindromatous types can be demonstrated. A given tumor may contain folliculoid, cylindromatous, and atypical areas.

Aschner, Plate, and Klaften (17) have described lipoid-rich cells in granulosa-cell tumors, and suggested that they may have a corpus luteum-like function, as evidenced by the occurrence of long amenorrhea, colostrum secretion, and functional stages in the endometrium in some of the cases. Klaften (17) also lays stress on the occurrence of corpus albicans-like structures.

The Brenner tumor is sometimes included with the granulosa-cell tumors. It is composed of epithelial complexes resembling ovarian follicles lying in a rather cellular connective tissue resembling normal
ovarian stroma. The epithelial cell complexes are composed of rather large, mostly polygonal cells with not very large, chromatin-rich nuclei; in part they form solid pegs in the stroma; more frequently they form a cell mantle of varied thickness which encloses a cavity. The cell row which encloses the cavity shows a regular border against the lumen. The cells of this row may be cylindric or flattened. The smallest cell complexes contain five to six cells, and are about the size of a primordial follicle. The cavities contain débris, including cell fragments. The epithelial cell nests are surrounded in most places by a concentric arrangement of connective tissue, which is more cellular than the surrounding connective tissue and recalls theca folliculi. The epithelial complexes often show a root-like branching.

**Prognosis**

The prognosis in granulosa-cell tumor is generally regarded as much more favorable than in other types of ovarian carcinoma. Three of Meyer’s (28) 33 patients died from metastases, while 19 remained permanently cured after operation. One of his cured cases was operated upon the first time at the age of five, and again three years later for a recurrence. Since then she has remained well for over ten years. Of 80 cases reviewed by Klaften (17) (his own, and cases from the literature), 6, or 7.5 per cent, were inoperable, and 4, or 5 per cent, had recurrences. Szathmáry in his review of 126 cases found recurrences in 13 cases, or about 10 per cent. Recurrences may be local, or there may be distant metastases. Soltmann reported a case with metastases to the first and second sacral vertebrae. In Klaften’s (18) nine-year-old patient, who died one year postoperatively, there were metastases in the brain. According to Klaften (17), granulosa-cell tumors are very radiosensitive.

**Related Tumors**

There is some confusion in the literature as to just where the “oophoroma folliculare” of Brenner stands in relation to the granulosa-cell tumor. The histological characteristics of this tumor have already been described. Meyer regards the Brenner tumor as distinct from the granulosa-cell tumor both in its histogenesis and in its clinical manifestations. He (29) thinks that it is derived from abnormal deposits of cells in the Walthard cell areas which have no potentiality to form granulosa cells, and that, in contrast to the granulosa-cell tumor, it is sexually functionless (30). Plant described eight cases of Brenner tumor, all of which were without clinical significance. Schiffmann, on the other hand, described two cases in which there was uterine bleeding in women past the menopause. In one of these cases the uterus was examined and found to show changes similar to those in cases of granulosa-cell tumor, only in slighter degree. TeLinde described a case in a sixty-two-year-old woman who gave a history of irregular bleeding. The endometrium showed hyperplasia and adeno-
carcinoma. In two of Brenner’s original three cases the tumors were small and were found incidentally at post-mortem examination, while in one there was a history of recent rapid growth of the tumor, which at operation was found to be almost as large as a man’s head.

Löffler and Priesel in 1932 reported six cases of “fibroma thecocellular xanthomatodes ovarii,” a tumor composed of cells resembling

![Fig. 1. Large Uterus with Thick Ragged Polypoid Endometrium, and Ovarian Tumor, in the Lower Pole of Which a Cyst is Visible](image1)

![Fig. 2. Cut Surface of Ovarian Tumor](image2)

The capsule is clearly distinguishable on one side. The tumor substance was partially crushed by the operative manipulations.

theca interna cells. Melnick and Kanter recently reported two similar cases, which they called theca-cell tumors of the ovary. These tumors exerted a distinct hormonal effect like that observed in cases of granulosa-cell tumor, indicating, in the opinion of these authors, that the theca cells play a rôle in the production of theelin. No hormone studies were made.
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REPORT OF A CASE

A white woman fifty-three years of age was seen in the tumor clinic of the Indianapolis City Hospital April 14, 1934, and was sent into the hospital. She complained of almost continuous vaginal bleeding for about a year, with loss of about twenty pounds in weight during that time. She had passed through the menopause six years previously, following which there was no bleeding for about a year. Irregular bleeding then began,

recurring every two to three months. The bleeding became more constant, and during the past year she had bled almost daily.

The menstes had begun at the age of fourteen, and were always regular. The patient had been married thirty-four years and had ten children, the oldest thirty-one years old and the youngest eleven. She had had a cholecystectomy in 1929. The family history was of no particular interest, except that her father had died of "enlarged heart."

Examination revealed a palpable movable mass in the pelvis and a uterus approximately the size of that of a four months' pregnancy. The blood pressure reading in millimeters Hg was 210 systolic and 110 diastolic. Erythrocytes numbered 4,280,000 per cubic millimeter of blood, and the value for hemoglobin was 77 per cent (Dare). A diagnostic curettage revealed a markedly hyperplastic endometrium. At operation, April 30, 1934, the uterus was found to be enlarged and there was a tumor of the right ovary. The body of the uterus and the right tube and right ovarian tumor were removed. The postoperative course was uneventful and the patient was discharged May 13, 1934.

The body of the uterus, with the attached right tube and right ovarian tumor (Fig. 1), weighed 318 grams. The endometrium was greatly thickened and appeared ragged and polyoid. The uterine wall measured 3.5 cm. in thickness. In the anterior wall in the fundic region was an area about 1.5 cm. in diameter having a whorled appearance suggesting adenomyoma. The ovarian tumor was approximately spherical in form and measured 6 cm. in diameter. It was pale yellow, and the surface was smooth except for a few nodular elevations. The cut surface was smooth, practically solid, and pale yellow except for a thin rim of grayish white tissue 2 to 4 mm. in thickness on one side.

FIG. 3. CYST RESEMBLING A GRAAFIAN FOLLICLE CYST

Note the wide border of cells enclosing the cavity, and the definite outward limitation of this border.
FIG. 4. **CELLULAR AREA NEAR THE TOP, CONTAINING SMALL FOLLICLE-LIKE STRUCTURES**

This area is just under the capsule.

FIG. 5. **CYLINDROMATOUS PORTION OF TUMOR**
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There was a somewhat lobulated arrangement of the tumor tissue. A few small cysts 1 mm. to 2 cm. in diameter, containing a pale yellow watery fluid, were observed.

Sections from the ovarian tumor show a rather typical histological picture of folliculoid and cylindromatous granulosa-cell tumor, the cylindromatous pattern predominating. Sections including the small cysts show a definite wide border of cells enclosing the cyst cavity, giving a picture recalling a graafian follicle cyst (Fig. 3). The cells of the outer row of the cell border are cuboidal or low columnar, while the other cells are polygonal. Structures resembling Call-Exner bodies are not observed in the cell border, and in this respect the folliculoid structure is not typical. In a few areas of the tumor a short distance under the capsule are large, closely packed masses of tumor cells containing small follicle-like structures about the size of a primordial follicle (Fig. 4), these structures consisting of a single row of cuboidal cells enclosing a cavity which contains some pink-staining homogeneous material and occasionally a cell nucleus. These cell masses are sharply limited in outline peripherally, the outer row of cells being cuboidal or low columnar and similar to the cells of the small follicle-like structures within. The remaining cells in these cell masses are polygonal and similar to the polygonal cells of

![Figure 6. Two Magnifications of Areas Showing Large Pale "Ova-like" Cells](image)

the wide cell borders of the larger follicle-like structures, or cysts, above described. The cylindromatous areas which make up most of the tumor mass show convoluted strands of polygonal tumor cells separated by a small amount of fibrous stroma (Fig. 5). Some portions of the tumor are neither cylindromatous nor folliculoid, but have a diffuse cellular structure with very little fibrous stroma. Small blood channels are fairly numerous but there are no areas of interstitial hemorrhage.

The tumor cells in general bear some resemblance to normal granulosa cells. They consist mostly of a nucleus which is round or oval, somewhat vesicular, fairly rich in chromatin, and stains dark blue with hematoxylin. Mitotic figures are not seen. The cytoplasm is small in amount and poorly defined in outline. It stains pale pink with eosin. Lying in the diffuse and cylindromatous areas near the capsule are many large pale cells which under low magnification recall ova (Fig. 6). The histological appearance presented by these areas is similar to that pictured by Ewing (9) as carcinoma of the ovary with ova-like cells. Under higher magnification the appearance of these large pale cells suggests hydropic degeneration (Fig. 7). A radial arrangement of tumor cells around these "ova-like" cells is not observed.

The capsule of the tumor is fibrous and resembles ovarian stroma, and this resemblance is strengthened by the presence of an occasional corpus albicans (Fig. 8). Obviously, what is left of the ovary is contained in this capsule. Corpus albicans-like
FIG. 7. AREA SHOWING "OVA-LIKE" CELLS

FIG. 8. TUMOR CAPSULE ABOVE, AND A MARGIN OF THE TUMOR BELOW

A corpus albidans is present in the capsule.
and corpus luteum-like elements, such as were described by Klaften (17), are not seen in the tumor substance.

The endometrium shows a marked degree of glandular-cystic hyperplasia, presenting the so-called Swiss cheese pattern on low magnification (Fig. 9). The area in the wall of the uterus suggestive of adenomyoma proves to be adenomyoma (Fig. 10).

Beginning twenty-four hours after operation the patient's urine was collected over a period of thirty-one hours, a total of 1045 c.c. being obtained. A Friedman test with

![Fig. 9. Hyperplastic Endometrium, Low Magnification](image1)

![Fig. 10. Portion of the Adenomyoma of the Uterus](image2)

10 c.c. of the first of this urine was negative. The remainder of the urine was concentrated by boiling and then extracted with ether. The ether was evaporated, and the residue taken up in 20 c.c. of water. Three castrated female mice previously shown not to have estrus cycles were injected subcutaneously with this material. The first mouse received four injections of 2.5 c.c. each over a period of twenty hours and showed a positive estrus reaction about twenty-four hours after the first injection. The second mouse received two injections of 2.5 c.c. each, separated by ten hours, and failed to show a positive estrus reaction. The third mouse received three injections of 1 c.c. each, over a period of fifteen hours, and showed a positive estrus reaction twenty-four hours after the
first injection. The urine remaining after the first ether extraction was re-extracted in the same way, and the extract so obtained was taken up in 10 c.c. of water. This material was injected subcutaneously into a castrated female mouse in 2 c.c. quantities over a period of twenty-two hours. A positive estrus reaction resulted forty-three hours after the first injection.

**Summary**

The literature on granulosa-cell tumor of the ovary is reviewed. A case of granulosa-cell tumor in a fifty-three-year-old woman six years past the menopause is described. There was a history of vaginal bleeding beginning about one year after the cessation of menstrual bleeding, continuing intermittently for four years, and then becoming almost continuous for about a year. Examination revealed a large uterus and a movable pelvic mass. At operation a right ovarian tumor 6 cm. in diameter, the right tube, and the body of the uterus were removed. The ovarian tumor proved to be a typical granulosa-cell tumor showing folliculoid, cylindromatous, and diffuse areas. The histological structure was predominantly cylindromatous. Grossly, the tumor was practically solid, showing only a few small cysts. The uterus was greatly hypertrophied, and the endometrium showed marked glandular-cystic hyperplasia. There was also an adenomyoma of the uterus. The urine collected over a period of thirty-one hours, beginning twenty-four hours after the operation, was shown to contain folliculin.

The diagnosis of granulosa-cell tumor in this case rests on the morphological characteristics of the tumor, the evidence of follicular hormone activity in a woman six years past the menopause presented by the large uterus, hyperplastic endometrium, and history of uterine bleeding, and the demonstration of folliculin in the urine.

**Bibliography**


