GRANULOSA-CELL CARCINOMA

A MALIGNANT OVARIAN TUMOR ASSOCIATED WITH ENDOCRINOLOGICAL EFFECTS

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There are two of the ovarian neoplasms which may properly be separated from the others and classified together on the basis of certain peculiar effects which the two produce. These are the arrhenoblastoma and the granulosa-cell carcinoma. They are grouped together because each appears to produce an hormone which is physiologically active in the body of the host. Earlier in this year the author presented a study on arrhenoblastoma (Norris, 1938) and many of the introductory remarks of that communication are equally applicable here.

At the outset a brief presentation of a case of granulosa-cell carcinoma will be made and attention will then be directed toward an analytical survey of this neoplasm and its effects.

CASE REPORT

Clinical History and Physical Findings: The patient was a married woman, fifty-two years of age, with a history of one pregnancy but no children. Menstruation had begun at fifteen years of age. The flow was heavy, coming every twenty-eight to thirty days and lasting for six or seven days. Two years prior to operation the menses became irregular, occurring only every two or three months. On one occasion—from February to December 1934—there had been no period at all. Following the December period there was again no flow until April 13, 1935. After that date the patient flowed every day and during the last two weeks profusely, passing many large clots. The remainder of the history is essentially negative.

The physical examination, June 3, 1935, was negative except for the pelvic findings. The uterus was moderately enlarged, firm, and nearly symmetrical. The left ovary was moderately enlarged.

On June 4 a diagnostic curettage was done and a relatively large amount of tissue obtained; a pathologic diagnosis of "hyperplastic endometrium" was returned. Pelvic laparotomy was undertaken and a subtotal resection of the uterus was done with a removal of the adnexal structures. The patient made an uneventful recovery but was not followed after leaving the hospital.

Pathologic Findings: The left ovary measures $7 \times 4.5 \times 4$ cm.; it is firm in consistence and presents a nearly smooth surface with slightly irregular contours. On the cut surface (Fig. 1) a rather dense fibrous capsule is seen and this surrounds tumor tissue, which is of a fleshy granular appearance and a grayish yellow color. Several small cyst-like cavities are present and these appear to be filled with blood.

The uterus is slightly enlarged due to the presence of four small intramural fibroids. The endometrium throughout the entire uterine cavity is thickened (Fig. 1). The right ovary and the fallopian tubes are grossly normal.

Microscopic Findings: Except for the fibrous capsular layer and some fibrous septa which divide the tumor, the normal ovarian stroma and structure have been completely replaced by tumor tissue.
The ovarian neoplasm is made up of broad sheets, bands, and narrow cords of epithelial cells. These epithelial structures tend to be arranged so as to surround spaces of variable size and shape as though in an effort to form follicles (Figs. 2 and 3). The epithelial elements are separated by a small amount of loose connective tissue in which a considerable number of blood vessels are present.

The epithelial cells of the tumor have relatively large amounts of cytoplasm; the nuclei are large, round, or ovoid, and for the most part are vesicular and poor in chromatin. Numerous mitoses are present. Not a few of the cells show vacuolization of their cytoplasm.

The endometrium is markedly increased in thickness (Fig. 6). The glands are numerous and greatly hypertrophied; many of them are irregular in outline with infoldings of their walls and some show huge dilatation. The glands show a tendency toward a stratification of the cells which make up their walls, and in some of these cells a moderate number of secretion vacuoles are present (Fig. 5). These cells are columnar in type. The endometrial stroma is much looser than normal (Figs. 5 and 6). In general the picture presented by this endometrium corresponds to that which is characteristic of the late proliferative phase of the menstrual cycle. The great thickness of the endometrium, however, and the cystic dilation of the glands, together with the other histologic features, make certain the diagnosis of hyperplastic endometrium.

**The Clinico-Pathologic Features of the Granulosa-Cell Carcinoma**

*Historical:* Although von Werdt in 1914 was the first to employ the name which we use today for the designation of this ovarian tumor, apparently von Mengershausen in 1894 and von Kahlden in 1895 had made earlier reports of similar cases. Von Kahlden interpreted the ovarian tumor in his case as an "adenoma of the graafian follicle." In 1901 Schröder reported cases of the von Kahlden type and following these earlier reports a few more cases were added. In recent years, however, since Robert Meyer called attention to the hormonal effects of the granulosa-cell carcinoma, great impetus has been given
to the study of these tumors, and the literature now contains the reports of many more than 100 cases.

**Definition:** The term “granulosa-cell carcinoma” originated with von Werdt in 1914. The granulosa-cell carcinoma may be defined as a malignant tumor of the ovary whose histologic structure commonly and characteristically shows the presence of granulosa-like cells which manifest a tendency to surround more or less typical follicles. The tumor is associated with signs and symptoms which may be ascribed to degrees of hyperestrinism. As with the arrhenoblastoma, it is these hormonal effects which give to the tumor its particular biologic importance.

**Incidence:** Although the granulosa-cell carcinoma is one of the less common ovarian neoplasms, it is by no means as rare as was once thought and apparently is far more common than the arrhenoblastoma. No figures are thus far available to express the serial incidence of this tumor.

**Age:** Instances of the granulosa-cell carcinoma have been reported from childhood to old age, but the greatest incidence appears to be in the fourth, fifth, and sixth decades, with the maximum number of cases grouped in the fifth decade. Relatively few cases have been described in women of advanced years or long after the menopause. On the other hand, a considerable number of cases have been reported before puberty, and in all of these there were manifestations of precocious sexual development.

**Clinical Symptoms and Signs:** The principal clinical manifestations of the granulosa-cell carcinoma depend almost entirely upon the age of the patient and the epoch of the female sexual cycle in which the tumor develops. Upon this basis the cases may be divided into three groups, in which the clinical pictures differ somewhat.

1. **Children before the Age of Normal Puberty:** It is in this group that the most dramatic symptoms are produced and precocious puberty results. Menstruation has appeared in girls as young as four years. Besides menstruation most of these young patients show a marked growth of the mammary glands and uterus and in many pubic and axillary hair has appeared and there has been precocious development of the external genitalia. In some cases the general body growth has increased and typical feminine contours have appeared.

2. **Women during Reproductive Life:** In this group the chief and most common symptom has been an increase in the duration of the menses and in the amount of flow. The periods, however, may become very irregular, and in a few cases long amenorrheic intervals may be noted (Habbe, 1931; Novak and Brawner, 1934). Novak has suggested that the appearance of bleeding and no bleeding phases may find explanation in reciprocal effects of ovarian and hypophyseal hormones. During the active reproductive epoch it is, of course, difficult to recognize changes in the breasts or external genitals. A diagnostic curettage usually reveals an hyperplastic endometrium.

3. **Women Past the Menopause:** After the climacteric the reappearance of uterine bleeding is always a dramatic symptom which may be due to some uterine neoplasm as well as to the granulosa-cell carcinoma. When due to the ovarian tumor the flow tends to approach normal periodicity, to be associated with endometrial hyperplasia, and with growth and secretory activity
Figs. 2–5. Ovarian and Uterine Tissue

Fig. 2 (above left) is a low-power photomicrograph of an area from the ovarian tumor, which has a tendency to form small and large follicles. Fig. 3 (above right) is another area (medium magnification) from the ovarian tumor, showing the cord-like pattern. Fig. 4 (below left) is a low-power photomicrograph of an area from the uterine wall. This section was taken from the operative specimen after curettage. Note the numerous enlarged glands deep in the mucosa adjacent to the myometrium. Fig. 5 (below right) shows a small area of endometrium obtained by curettage to show the character of the glands (high magnification). Note the hyperplasia and stratification of the epithelial cells and the presence of a few secretion droplets. The loose stroma is well shown.
(colostrum) of the breasts (Müllerheim, 1928; Plate, 1933). Of special interest are the observations of Klaften (1932) and Plate (1933), who have described an associated hirsutism and virilism.

The general symptoms and signs are those of other malignant tumors and are dependent in part upon the size of the tumor and upon the location and extent of metastases. Severe degrees of anemia may result from the profuse and prolonged menstruation, and cachexia or emaciation may develop.

Clinical Course and Prognosis: Although the menstrual phenomena may be intermittent and irregular, the general course of the disease is continuous and progressive. The untreated cases go on to death from malignant metastases. The prognosis, therefore, is largely determined by the duration of symptoms before the patient presents herself for operation. In general the tumor tends to grow slowly and to metastasize late, so that with the proper treatment in operable cases a good prognosis may be given.

Treatment: As in other malignant conditions the early surgical removal of the primary tumor offers the only hope of permanent relief. The study of a larger number of cases and the observation of the postoperative course in these has provided indisputable evidence of the malignant tendencies of the granulosa-cell carcinoma. Therefore, except in children and possibly in young women, where the conservative removal of the neogenic gonad alone may be justifiable, the operative procedure should regularly be of radical nature. Radiotherapy may be used in the treatment of inoperable or recurrent tumors, or it may be employed as a preoperative or postoperative adjunct to surgery.

Postoperative Course: If complete surgical extirpation of the tumor can be accomplished at an early period the postoperative result is good. Such an operation relieves the symptoms by restoring a more normal hormonal balance and the effect is especially dramatic in those cases where the lesion has produced precocious puberty. Instances have been reported in which the symptoms had been relieved postoperatively only to return again with the recurrence of the tumor.

Clinical Diagnosis: As a rule, the tumor can be recognized by pelvic examination, but in women seen during the reproductive epoch the identity of the growth has usually not been suspected before a report on the microscopic pathology has been returned. However, the association of an adnexal tumor with menstrual disturbances and the demonstration of an hyperplastic endometrium should make a presumptive preoperative diagnosis possible even in these cases.

"It is in childhood and in the postmenopausal years that the preoperative diagnosis of the nature of the tumor can most often be made, at least presumptively. This is because of the physiologic and biologic effects produced by the growth, which stand out sharply in patients at these ages. . . . If an ovarian tumor is demonstrable in a child with precocious menstruation and puberty, it is very likely to be of the granulosa-cell type. Again, if a tumor is found in a patient well beyond the menopause, associated with periodic and perhaps pseudomenstrual bleeding, it is almost sure to be a granulosa-cell cancer. The likelihood is converted into almost absolute certainty if a diagnostic curettage yields a frankly hyperplastic endometrium. In both these groups hormone studies are of even greater value than in the case of tumors
In this section the full thickness of the endometrium is shown. Note the large number of glands and the extreme variation in size of these. Many of the glands show plications on their walls. The loose, succulent endometrial stroma is well shown.

encountered in patients during reproductive life.” (Novak and Brawner, 1934.)

In girls before the age of normal puberty there are two other conditions which need to be thought of in making a differential diagnosis. These are: first, degrees of pseudohermaphroditism associated with anomalous states of development, and second, those conditions which are at times produced as a part of the suprarenal-cortical syndrome.
In women of more advanced age groups the differential diagnosis is usually directed toward the exclusion of benign or malignant growths in the uterus.

Pathology: Without exception the cases of granulosa-cell carcinoma which the literature contains appear to be based upon the study of surgically removed specimens. I know of no case which has come to autopsy, had an examination of all the tissues, and been reported. In many of the cases diagnostic curettage has been done, and in some hysterectomy. Most of the pathologic investigations have been based, therefore, upon the study of the primary tumor alone, while some cases have provided the opportunity to study the endometrium or the uterus and the non-neogenic ovary as well. There is a great need for a thorough study of the general pathology in this disease; it may be that complete post-mortem examinations will greatly extend our knowledge of the condition. It seems quite possible that almost as remarkable changes might be found in the endocrine glands associated with this tumor as have been described in those from our case of arrhenoblastoma (Norris, 1938).

Regularly only one of the ovaries is involved by this tumor. The opposite, or non-neogenic ovary, is unaffected by the presence of the tumor and it appears as the gonad of a female of corresponding years.

Granulosa-cell carcinomas are tumors of varying degrees of malignancy. They have a tendency to invade, to metastasize, and to recur postoperatively. Most of the recurrences have been local in the pelvis, but metastatic implants have been described in the peritoneum, the liver, and the skeleton (Aschner, 1922; Klaften, 1932; Soltmann, 1932; Bagger, 1933; Novak and Brawner, 1934). Although the granulosa-cell carcinoma may grow slowly and metastasize late, it is always a cancer, and the suggestion of Novak and Long (1933) that this group of neoplasms be referred to as “granulosa cell adenomas” is misleading and a valueless multiplication of terms. Certain of the reported tumors have been only a few millimeters in diameter, while others have grown to huge proportions. Most have been recognized when of moderate size and the tumor has then commonly been an ovoid or reniform mass, the outer surface of which is usually smooth but may be indented by irregular gross lobulations. The majority have been solid tumors whose cut surfaces have had a fleshy, granular appearance, and have been divided by fibrous trabeculae; less commonly small cysts—rarely large cysts—have been noted.

The histologic structure of the granulosa-cell carcinoma is variable within wide limits. In some tumors the structural pattern is made up of follicle-like structures (folliculoma malignum of von Kahlden) which may be lined with one or more layers of cells or may be outlined by stratified epithelium similar to the granulosa-cell layer of the normal ovarian follicle. Such structural patterns as these are, of course, those which are most easily recognized microscopically. On the other hand a variety of less well organized patterns may be found; broad epithelial sheets, irregular anastomosing cords or a loose sarcoma-like arrangement of the cells may be characteristic. Any of these patterns may predominate or several of them may be mixed in the same tumor. No matter what the structural arrangement, there tends to be a morphologic resemblance of the constituent cells to granulosa cells, and the cytological types may, therefore, afford evidence of the tumor’s nature. Typical histologic pictures are easily recognized, but many of these tumors show such varied
and atypical patterns as to make their exact recognition impossible. Not a few are too atypical in structure to allow of a diagnosis upon the basis of microscopic anatomy alone; and in such cases the pathologist’s interpretation must needs be guarded unless a knowledge of the characteristic clinical picture is had. Thus granulosa-cell carcinoma is best regarded not as a separate pathologic lesion but rather as a clinico-pathological entity. Certainly there is nothing to be gained at present from any effort to subdivide the cases into groups upon the basis of histologic structure, or from the insistence upon special descriptive names (folliculomatous, parenchymatous, cylindromatous, adenomatous, sarcomatous, etc.). At present such terms can have no more than descriptive significance when applied to individual tumors and they should not be employed for the designation of separate pathological groups.

“The degree of histologic malignancy in granulosa cell tumors is quite variable and does not seem to be clearly related to the degree of clinical malignancy. In some tumors there is little evidence of anaplastic change, and mitoses may be few. In others there may be marked disparity of cells and nuclei, hyperchromatosis, and numerous mitoses. The tumors are usually quite vascular and often exhibit marked dilatation of the lymph vessels.” (Novak and Long 1933.)

Certain authors have attempted the further subdivision of the granulosa-cell carcinomas. Löffler and Priesel (1932), Melnick and Kanter (1934), and Brosig (1936) have considered the separation of those tumors having a more or less sarcomatous structure into a special group. This group they would designate by the term “thecoma” or by the more complete name of “fibroma thecocellulare xanthomatoses ovarii.” Along the same line Lecène (1932), Moulonguet-Doléri (1927) and Plate (1933) have been impressed by the lipoid content of the tumor cells and have suggested the term “folliculome lipidique” for the group. Novak and Long (1933) have also reported a case (their case 28) which they assign to this latter group, in which they found areas in the endometrium that suggested a progestin effect.

There seems as yet no sufficient reason for any subdivision of the granulosa-cell carcinomas even on the bases suggested in the preceding paragraph. One needs to remember the frequency of fatty metamorphosis in tumor cells of whatever nature or derivation, and to guard against wishful interpretation of meager findings. It does seem, however, that the suggestions of these authors should be taken seriously and every possible effort made to determine whether or not there is any progestin formation by certain of these tumors. The finding of fat and lipoid in the tumor cells and slight or local progestin-like alterations in the endometrium are not sufficient reasons for subdivision of the general group of granulosa-cell carcinomas. The biologic demonstration of progestin in extracts from tumors, the presence of easily recognized, extensive premenstrual changes in the endometrium, and the finding of more typical lutein structure in the tumor are needed before a justifiable subdivision of the group can be made.

Pathogenesis of the Granulosa-cell Carcinoma

Cohnheim’s theory of embryonic cell rests has been elaborated and adopted by Meyer as an explanation for the origin of the granulosa-cell carcinoma.
He has contended strongly for this theory, and his ideas have apparently come to be almost universally accepted in the literature. He has based his point of view upon the following considerations. In the first place, granulosa-like rests have been found in the ovaries of children and even in those of adult women. In the second place, the granulosa-cell carcinoma may occur in women of advanced years, when the normal follicular tissue has largely disappeared. In the third place, Meyer has contended that the epithelium of the ovarian follicle is to be thought of as a satellite tissue, depending for its life on the life of the ovum, to which it seems to be physiologically subservient. These reasons I believe are not adequate to explain the development of this tumor. Cell rests in the ovary are far more common than granulosa-cell carcinomas. Again, it is not necessary to hypothesize cell rests to explain this tumor's appearance in older women, for remnants of adult follicles, or even other parts of the gonad, may provide an acceptable source. We have seen how the follicular epithelium and the interfollicular stroma both come from the original ovarian mesenchyme (Norris, 1938). Finally, there is no certain proof that the follicular cells depend so closely upon the presence of the ovum for their life; in fact, it appears to be after the discharge of the ovum that the follicular cells take on their most active growth and differentiation in the formation of the corpus luteum. The difficulties encountered by the theory of embryonic cell rests in relation to tumor formation have been most concisely stated in the following paragraph by Bell.

"The objections to Cohnheim's theory are: (1) A great many tissue rests do not produce tumors. They may atrophy or grow only to a limited extent. (2) There is no explanation in Cohnheim's hypothesis of the stimulus to growth. Mere displacement is not sufficient. Tissues artificially displaced do not become tumors. (3) The theory is not generally applicable, since it can be shown that many tumors develop from normal tissues. Cohnheim's theory helps us to understand the situation of many tumors but does not explain why growth occurs. A fetal rest must receive some stimulus before it begins to grow just as in the case of normal tissue cells." (Bell, 1938.)

Hormonal Pathology: That the granulosa-cell carcinoma produces estrin seems to have been satisfactorily demonstrated. Schuschania (1930) studied a case in which large amounts of estrin were excreted in the urine and stool before operation and none was excreted about two months after the tumor had been removed surgically. Moreover, the chief clinical phenomena associated with this tumor, especially in children and in older women, are those ascribable to the presence of estrin, while the endometrial changes are those produced by abnormal amounts of this substance.

Novak (1933) says: "Tumors arising from such granulosal tissue, already differentiated along female lines, have the capacity of hyperfeminizing the patient, for the constituent cells retain the physiologic function of producing the female sex hormone." This statement is quoted here for the purpose of calling attention to two points. The term "hyperfeminizing" does not seem well chosen, for the clinical effects in this condition are not those of increasing or intensifying the female characteristics. The effects are only those brought about by the action of estrin, and such differences as are noted from patient to patient seem to depend for the most part upon the age of the individual in
which the tumor develops. Possibly some of the effects depend also upon the amount of estrin which is produced. Such quantitative observations upon the hormone as we have seem to indicate that estrin is present in abnormally large amounts. For these reasons it would be proper to regard the physiology of the granulosa-cell carcinoma as a condition of hyperestrinism and not one of hyperfeminization. Again we need to caution that, although estrin is accepted as the female sex hormone, it is well to hesitate before reasoning that because a tumor produces estrin it must have its origin in cells "differentiated along female lines." We know that estrin occurs widely in nature and that in certain male tissues it may be present in large amounts.

**Summary and Conclusions**

1. A case of granulosa-cell carcinoma is reported.
2. The world's medical records include the reports of many more than 100 cases of granulosa-cell carcinoma.
3. The granulosa-cell carcinoma may be defined as a malignant tumor of the ovary whose histologic structure commonly and characteristically shows the presence of granulosa-like cells which manifest a tendency to surround more or less typical follicles. The tumor is associated with signs and symptoms which may be ascribed to degrees of hyperestrinism.
4. The granulosa-cell carcinoma may develop in any of the decades of life and the principal clinical manifestations vary with and depend almost entirely upon the age of the patient and upon the epoch of the female sexual cycle in which the tumor develops. In children the granulosa-cell carcinoma is a cause of precocious puberty. In the older age groups the effects are chiefly concerned with menstrual phenomena.
5. The general course of the disease is continuous and progressive, and untreated cases go on to death from malignant metastases.
6. Early surgical removal of the primary tumor is the only hope of permanent relief; in general the operative procedure should be of radical nature. The postoperative result is good, and the symptoms disappear if the tumor can be removed.
7. The differential diagnosis upon clinical grounds is not difficult in children or in women past the menopause but may be impossible in women seen during the reproductive epoch.
8. The histologic structure of the granulosa-cell carcinoma is variable within wide limits; the pattern varies from typical follicle-like structures, broad epithelial bands, and narrow cords, to sarcoma-like pictures. There seems to be no advantage in the subdivision of the granulosa-cell carcinomas on the basis of their differing histology.
9. As yet the evidence is too meager to make significant the separation of the so-called "thecoma" or the "fibroma thecocellulare xanthomatodes ovarii" as distinct groups.
10. Cohnheim's theory of embryonic cell rests, the theory elaborated and adopted by Robert Meyer, as an explanation for the origin of the granulosa-cell carcinoma cannot be accepted as adequate.

**Note:** Thanks are due H. W. Morris for the photographic work on this paper.
Bibliography