OVARIAN DYSGERMINOMA

SEATON SAILER, M.D.

(From the Pathology Department of the Medical College of the State of South Carolina, Charleston, S. C.)

A malignant tumor of the ovary histologically similar to the testicular seminoma was originally identified by Robert Meyer as arising from undifferentiated sex cells of the primitive mesenchyme of early embryonic life (1). Meyer gave to this tumor the name dysgerminoma and called attention to its tendency to occur in young women and to its frequent association with hermaphroditic or pseudo-hermaphroditic states. Of late increasing numbers of observations on the behavior and occurrence of the dysgerminomas have been recorded. Seegar (2) in 1938 collected 79 cases from the literature, exclusive of 23 cases described by Meyer as associated with hermaphroditism, and added 19 observations of his own. The same year Novak and Gray (3) contributed another 17 cases. These together with sporadic reports (4) to date bring the total to more than 160.

The assumed rarity of the dysgerminoma thus seems somewhat questionable, especially as many observations undoubtedly remain unrecorded, while other examples are incorrectly diagnosed. Klaften (5) reported an incidence of 3.1 per cent among 188 primary malignant tumors of the ovary. In reviewing the surgical files of the Pathology Department of the Medical College of the State of South Carolina for the past ten years we have found 5 dysgerminomas among 80 primary malignant ovarian neoplasms, an incidence of 6.2 per cent. In the same group there were 14 granulosa-cell tumors, or 17.5 per cent. The great majority of the remaining tumors were either cystic or solid papillary adenocarcinomas.

Dysgerminomas appear most frequently in the right ovary, in patients below the age of twenty years. While their origin has not been established beyond question, Meyer's theory is generally accepted. He ascribed their development to nests of proliferating undifferentiated mesenchymal cells in the primitive genital gland common to both sexes in the early embryo. This condensation of cells, known as the genital ridge, bulges into the celomic cavity on the ventro-medial surface of the urogenital fold. These germ cells may be regarded as sexually indifferent since the formation of medullary cords is not yet apparent. The absence of masculinizing or feminizing effects in association with the dysgerminomas is in keeping with the neutral character of the early undifferentiated cells participating in their formation. Such effects may be observed with tumors arising in cell groups derived from a more advanced stage of embryonal sex development, as the arrhenoblastomas and granulosa-cell tumors.

The predilection of the dysgerminoma for the right ovary is in accord with the relatively slow and less complete development of that organ. Seegar remarks that studies in comparative anatomy demonstrate that the right ovary
in birds remains undeveloped throughout life. Thus, if undifferentiated tissue is left behind, the probability of its occurrence is greater on the right side, and this becomes the more likely site of tumor development. The frequent association of hermaphroditism or pseudo-hermaphroditism with ovarian dysgerminoma also supports the theory of arrested gonadal development, as these conditions are not infrequently associated with the retention of immature cell types. Removal of the tumor has no effect on the genital anomaly.

Little evidence has been advanced to support the alternate theory of origin of the dysgerminoma as the one-sided development of a teratoma.

Studies of gonadotropic substances in the urine of patients with dysgerminoma are incomplete and few quantitative assays have been reported. Spielman and Morton (6) found prolactin A in extracts of the tumor in their case in a sixteen-year-old colored girl, but estrogenic hormone was completely lacking. While the latter observation is to be expected in a tumor derived from sexually indifferent cells, the presence of the prepubertal hormone cannot readily be explained. An increase of this hormone has been reported in patients suffering from amenorrhea. Dysgerminomas, however, have been recorded in women with a history of full-term pregnancies either prior to the appearance of the neoplasm or subsequent to its surgical removal (7). The association of a normal pregnancy with the tumor has also been observed (8). Clinically a rapidly enlarging abdominal tumor with or without pain is an early complaint.

Grossly the tumors are usually large, nodular, and enveloped in a shiny tendinous-appearing capsule. Their consistency is firm and elastic, though semi-solid and soft forms may result from degenerative changes. The microscopic appearance is quite distinctive and a rather constant uniformity of structure is displayed. The tumors are composed of broad sheets and columns of large round cells having an abundance of lightly acidophilic cytoplasm and dark hyperchromatic nuclei. Nucleoli are usually visible and mitoses are numerous. Delicate strands of connective tissue support the tumor cells and small lymphocytes are usually abundant. Coarser strands of connective tissue sometimes divide the tumor into small nests or islands. Pseudo-tubercles formed by collections of epithelioid cells, fibroblasts, and scattered giant cells have been reported and their significance has been variously interpreted. Some observers have found an associated adnexal (9) or intestinal (10) tuberculosis. Others, noting the same changes in tumors unassociated with tuberculosis, have been unable to demonstrate tubercle bacilli. The arrangement of the epithelioid and giant cells suggests tuberculous granulation tissue rather than discrete tubercles with caseation necrosis. Often these cells are intimately intermingled with tumor cells. Schiller (11) believes this to be a stromal reaction to disintegrating tumor cells, although transition forms between tumor and giant cells have been observed. Föderl (12), on the other hand, found this reaction in tumor thrombi lying within the lumina of small blood and lymph vessels containing no stromal elements. Under these circumstances a derivation from tumor cells or from transformed endothelial cells must be assumed. Föderl points out that, inasmuch as dysgerminoma cells are mesenchymal derivatives, the epithelioid cells may represent either a proliferation of tumor cells of mesenchymal origin differentiating in a “false”
connective-tissue direction or a maturation of mesenchymal cells closely related histogenetically to the dysgerminoma cells.

Granulosa cell-like groups have also been reported within dysgerminomas and in some instances have assumed a folliculoid structure. Whether these areas represent mesenchymal cells which have not lost the power of differentiating and whether they are capable of hormonal production cannot be definitely stated. Tietze (13) reported a dysgerminoma occurring in a girl of ten years with precocious sexual development whose advanced secondary sex characteristics regressed after the removal of the tumor. Microscopic examination of the growth, however, showed no granulosa-cell areas with folliculoid arrangement.

Föderl encountered a dysgerminoma in a fifty-one-year-old woman in which a considerable portion of the tumor was composed of granulosa cells. The uterus had been removed three years earlier because of functional bleeding and the effect of the tumor on menstruation could not be determined. The dysgerminoma seemed to be the malignant portion of the tumor and had metastasized widely. Another case, recorded by the same author occurred in a fourteen-year-old girl who had never menstruated. Bilateral dysgerminomas, together with the uterus, were removed at operation. The patient was seen two years later and showed well developed secondary sex characteristics and complained of periodic pain occurring every twenty-five to twenty-eight days at the site of a large liver metastasis. This tumor and the periodic pain disappeared under x-ray therapy. A later recurrence in the pelvis, associated with pain of the same type, also disappeared following irradiation. Two Aschheim-Zondek tests were negative, but quantitative hormonal studies on the blood and urine were not performed. The author believes that the metastatic tumor tissue was functionally active under the influence of the anterior pituitary gland. The tumor tissue removed at operation was extensive and no folliculoid areas were noted in the sections examined.

The interpretation of these histological findings and their physiologic importance await further investigation.

While little can be concluded from the cases to be reported here, their biologic behavior and histologic structure appear to warrant recording.

Case Histories

Case I (Dr. C. B. Epps, Sumter, S. C.): L. S., a ten-year-old colored girl, was admitted for observation on March 18, 1938, with a large mass in the left lower abdominal quadrant associated with slight pain. The patient was well developed but somewhat thin and anemic. She had never menstruated. No genital anomalies or other physical abnormalities were present. The uterus was infantile and displaced to the right by a large tumor occupying the left side of the pelvis. At operation the left adnexa, containing a firm, nodular, oval ovarian tumor, 14 X 8 X 8 cm., was removed. No extension of the tumor through the capsule was observed at operation nor were there any lymphatic metastases.

The cut surface of the tumor was grayish-white and glistening. No remnants of ovarian stroma were discernible microscopically. The tumor was composed, for the most part, of diffuse sheets of large round cells with deeply staining central nuclei. Mitoses were numerous. In occasional areas connective-tissue strands divided the growth into discrete nests and columns. Abundant lymphoid cells infiltrated the stroma (Fig. 1). A few scattered tubercle-like structures were present in the cellular portion of the tumor.

The postoperative course was uneventful. Deep x-ray therapy over the abdomen was
FIG. 1. LARGE ROUND CELLS CLOSELY ARRANGED, WITH ABUNDANT INFILTRATION OF SMALL LYMPHOCYTES. × 300

FIG. 2. METASTATIC TUMOR NODULE IN OMENTUM CONTAINING PSEUDO-TUBERCLES. × 300
begun and a total of 2500 r administered, after which the patient failed to return for treatments. On April 24, 1939, she was again seen with swelling of the abdomen and pain in the lower quadrants. Fluoroscopic examination of the chest revealed considerable fluid in the right pleural cavity. Several round discrete areas of increased density in the base of the left lung were believed to be metastatic tumors. A laparotomy was performed and extensive infiltration of the tumor was found in the uterus, right tube, and ovary. The pelvic lymph nodes and omentum were also massively involved, but the liver appeared uninvaded. A portion of the omental tissue was removed for study and the wound was closed. Microscopic study revealed growth of the same type as in the previous specimen with numerous tubercle-like areas and granulation tissue intimately intermingled with the tumor cells. In a few zones there appeared to be transition forms between the dysgerminoma cells and the epithelioid cells of the pseudo-tubercles. Both foreign body and Langhans' giant cells were observed (Fig. 2).

Following the second operation the patient became progressively emaciated and weak. She died Nov. 6, 1939, approximately twenty months following removal of the original tumor.

**Case II** (Dr. James McLeod, Florence, S. C.): D. K., an unmarried white girl of eighteen years, was admitted for observation Feb. 20, 1939, complaining of a sense of weight in the pelvis, particularly on leaning forward, of three months' duration. This was progressive in character and in the past six weeks the lower abdomen had become enlarged. The menses had always been regular and painless until the last two periods, when the patient suffered from severe dysmenorrhea. There was also a history of increasing constipation. The patient was well developed and well nourished and blood and urine studies were negative. A firm, fixed, nodular mass was palpable in the right side of the pelvis, extending to the level of the umbilicus.

At operation an oval, nodular tumor, covered by a firm capsule, was removed. It measured 20 × 15 cm. and had a grayish-white homogeneous cut surface. The left adnexa and uterus appeared normal.

Microscopically the tumor was composed almost entirely of large round cells with deep-staining nuclei, showing numerous mitoses (Fig. 3). The stroma was scanty and lymphoid cells were few in number. A few pseudo-tubercles but no granulosa-cell areas were present.
The postoperative course was without complication and no radiation was given. At the present time the patient is symptom-free and in excellent condition, eight months following operation.

CASE III (Dr. J. H. Cathcart, Gaffney, S. C.): I. C., an unmarried white girl of fifteen years, was admitted on Sept. 24, 1936, complaining of a rapidly enlarging painless mass in the lower abdomen, of two weeks' duration. She had had three normal menstrual periods, at twenty-eight day intervals, lasting eight days, followed by amenorrhea for two months prior to admission. Physical development and nourishment were good. The uterus was small and pushed up against the pubis, a little to the left of the mid-line. A firm symmetrical mass extended from the cul de sac on the right side to three finger breadths above the umbilicus.

A round, semi-solid tumor of the right ovary 30 cm. in diameter and weighing 3075 gm. was removed. The left tube, ovary and uterus were normal. The tumor was encapsulated and on section was grayish-white, soft, and moist, with numerous areas of necrosis. No enlarged lymph nodes were present in the mesentery or along the posterior peritoneum.

Microscopically the tumor was extremely cellular and showed numerous areas of necrosis and fresh hemorrhage. The cells were uniformly large and mitotic figures were quite prominent. Little stroma was present and about the tumor cells were groups of small lymphocytes. In occasional areas small tumor thrombi were found within dilated lymph vessels (Fig. 4).

Convalescence was uneventful, and regular menstruation was re-established three months after operation. No postoperative radiation was administered. At the present time, three years following removal of the tumor, the patient is in excellent condition.

CASE IV (Dr. R. L. McCrady, Charleston, S. C.): E. A., an unmarried colored girl of seventeen years, was admitted Nov. 6, 1933, complaining of intermittent dull pain in both lower abdominal quadrants, of three weeks' duration, and sharp pain over the same area three days prior to admission. A second attack of pain, of greater severity, occurred on the day of admission and the patient was brought to the hospital in an ambulance. She appeared well developed and well nourished but anemic. Menstruation had always been of
the regular twenty-eight-day type lasting three or four days, but the last two periods had been missed. Examination of the blood showed hemoglobin 58 per cent. The Wassermann reaction was 4+. Pelvic examination revealed a large solid tumor on the right side.

An oval encapsulated tumor of the right ovary, 17 × 10 cm., was removed with the corresponding tube. The tumor was rather soft and on section had a mottled grayish-yellow and red appearance. The uterus and the left tube and ovary appeared normal.

Microscopically the tumor was found to contain extensive areas of hemorrhage separating and destroying broad sheets of large, round, closely packed tumor cells. Mitoses were numerous. Small portions of the tumor were divided by dense strands of fibrous connective tissue containing small blood vessels. Lymphoid tissue was scanty and appeared confined to the connective-tissue strands. No tubercle-like structures, granulosa cells, or recognizable ovarian tissue were seen (Fig. 5).

Postoperative recovery was uneventful. No postoperative radiation was given. The patient is well and symptom-free to date, six years after removal of the tumor.

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**CASE V (Dr. Riddick Ackerman, Walterboro, S. C.):** N. B. S., a white married woman of twenty-one years, was admitted for observation on Nov. 28, 1935, with a history of a severe attack of pain in the right lower abdominal quadrant two months prior to admission. This lasted two hours and recurred on the day of admission. Menstruation had begun at thirteen years, occurring regularly every twenty-eight days, lasting four to five days. The patient had one child, two years of age and in good health. There had been no miscarriages. A large firm tumor was palpable in the right adnexal region. The uterus and left adnexa appeared normal.

A firm, oval, grayish-white tumor of the right ovary, measuring 8 × 5 cm., was removed with the corresponding tube. The cut surface was glistening, gray, and homogenous.

Microscopically a small rim of ovarian cortex containing graafian follicles and ova was discernible. The remaining tissue was composed mainly of loosely arranged, large round tumor cells supported by delicate connective-tissue strands. Rather abundant lymphoid tissue infiltrated the tumor cells and stroma and formed solid aggregates. Mitoses were fairly prominent. One area in the center of the tumor showed a well formed graafian follicle completely surrounded by large tumor cells (Fig. 6). In addition, occasional heaps of granu-
Lososa cells showing a follicle-like structure were found merging into the tumor tissue (Fig. 7). No pseudo-tubercles were noted. Occasional lymph vessels contained tumor cells (Fig. 8).

The postoperative course was uneventful. No radiation was given. Menstruation was re-established three months after operation, and two years later the patient became pregnant. The child is living and well. Another child was born at term in September 1939. At the
present time, four years after operative removal of the tumor, the patient is in good health and apparently cured. She is able to nurse her baby and carry on her normal activities.

**DISCUSSION**

The predilection of the tumor for the right ovary and the age incidence in this small group are characteristic of the dysgerminomas. The short duration of symptoms relative to the size of the tumor is indicative of their rapid growth. Individual differences in growth potentiality are not reliably reflected in the microscopic appearances. Thus in Case I extensive metastases were present one year following the removal of the tumor, and the patient died in spite of irradiation after a total illness of twenty months, while in Case IV, with an almost identical histologic appearance, the patient is alive and well six years after operation. The number of mitoses per field appears an unreliable index of growth. Clinically, the best indication of the degree of malignancy is the amount of infiltration of the tumor capsule at operation or extension into the adjacent lymph nodes. Dissemination of the tumor is usually confined to the peritoneal cavity, following the lymphatic route. Widespread metastases are distinctly uncommon, though discrete liver and kidney lesions have been reported. Seegar places the mortality between 35 and 60 per cent, with a slightly higher rate of recurrence.

Whether misplaced rests of undifferentiated sex cells capable of producing dysgerminomas may occur outside the ovary has been questioned. Schiller's case (14) of a dysgerminoma occurring in the wall of the uterus of a forty-seven-year-old woman who showed no ovarian tumor indicates that embryonal rests may occur along the course of the müllerian ducts. Such cases, however, appear to be extremely unusual.
The physiological significance of the granulosa-cell nests among the dysgerminoma cells awaits further biochemical study.

**SUMMARY**

1. Five cases of ovarian dysgerminoma are reported, in young women between the ages of ten and twenty-one years. Four of the tumors occurred in the right ovary and one in the left. This group represents an incidence of 6.1 per cent among a series of 80 primary malignant ovarian tumors.

2. The microscopic appearance of these tumors, including the number of mitoses, appears to be an unreliable indicator of growth potentiality. All of the tumors studied were very cellular and showed a striking resemblance to testicular seminomas. One tumor, in a ten-year-old colored girl, recurred a year following removal, with extensive pelvic, peritoneal, and probable lung metastases. Death occurred one year and eight months after removal of the primary growth. Three other patients are living and well without evidence of tumor, three, four, and six years after operation. The remaining patient is symptom-free eight months following removal of the tumor. None of those still living received x-ray therapy either before or after operation.

3. One patient had a child born two years prior to removal of the tumor, and had two normal full-term pregnancies two and four years, respectively, following operation.

4. The histogenesis of these tumors and some of their microscopic components are discussed.

**BIBLIOGRAPHY**