HETEROLOGOUS MESODERMAL TUMORS OF THE UTERUS
REPORT OF A NEOPLASM RESEMBLING A GRANULOSA CELL TUMOR *

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Heterologous tumors of the uterus are not extremely rare. By far the most common neoplasms in this group are the mixed mesodermal tumors which occur in both the body and cervix of the organ.[1] At present, it is impossible to say with certainty whether the tumors occurring in the cervix differ fundamentally from those confined to the fundus. Pathologically, they are very similar.

Mixed mesodermal tumors are monodermal in origin and should be distinguished from the trigerminal teratomas, which are extremely rare. Morphologically, the former are sharply demarcated polypoid growths which occupy a submucosal position in the uterus and are composed of heterotopic malignant cells of various types. Embryonic myxomatous tissue is present in all of these tumors, and in many of them hyaline cartilage, striated muscle, bone and fat are to be seen. Many of the cells are well differentiated and the degree of malignancy is out of all proportion to the histological appearance. The prognosis is uniformly grave, most of the patients succumbing during the first year.

Many theories regarding the origin of these neoplasms have been proposed. The simplest explanation is that of neoplastic metaplasia.[2] However, it is extremely unlikely that adult tissues normally present in the uterus can be dedifferentiated into mesodermal derivatives which are normally not seen in that organ. Wilms [3] is of the opinion that these tumors arise from undifferentiated mesodermal cells which are displaced from the lumbar region during the descent of the Wolffian body. Lebowich and Ehrlich [4] have objected to this theory on the basis that no proved cases of this type of tumor have been reported as having developed along the course of the Wolffian ducts. In the light of our present knowledge, it appears most likely that these tumors originate from indifferent mesodermal cells which have retained their capacity for differentiation into mesodermal tissues of various types.[5]

Several case reports of tumors of this type are to be found in the recent literature, and excellent reviews of the subject have been given by Lebowich and Ehrlich,[4] Glass and Goldsmith [6] and Liebow and Tennant.[7] The purpose of this paper is to report the unusual case of a heterotopic mesodermal uterine neoplasm which possessed all of the morphological characteristics of a granulosa cell tumor. The case is of

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interest further in that it affords additional support for the contention of Fischel,[5] and others, that the granulosa cells are derived from the mesenchyme and not from the celomic epithelium as is ordinarily taught.

Report of Case

A white female, 44 years old, was admitted to the North Carolina Baptist Hospital on January 25, 1943, complaining of menorrhagia, a sense of pressure in the lower abdomen, and leukorrhea which was exaggerated immediately following menstruation.

She began menstruating at the age of 16 years and her periods occurred every 28 days with a duration of from 4 to 6 days. About 3 years before, she began to menstruate more frequently than formerly, and the interval between periods was reduced to 24 days. Concurrently, an increase in the duration and amount of flow was noted, menstruation now lasting from 6 to 8 days. She had been pregnant seven times and had had two miscarriages and five normal deliveries.

The physical examination revealed a fairly thin woman in no apparent distress. Her temperature was 37° C.; pulse, 87 per minute; respirations, 22 per minute; and blood pressure, 180 mm. of Hg systolic, 78 diastolic. The thyroid gland was normal in size and position. The breasts were atrophic and no masses were felt. On auscultation a soft apical systolic murmur was heard. Positive physical signs were not elicited from the lungs. The abdomen was soft and there were no masses or tenderness.

Pelvic examination revealed normal external genitalia and a parous outlet. A cystocele and rectocele were present. The uterus was normal in size and was freely movable; a third degree retroflexion was present. No masses were palpable in the adnexa. The cervix showed slight erosion around the external os but was otherwise not remarkable.

The hemoglobin was 76 per cent (Sahli) and the leukocyte count showed 5,200 cells per cmm. The studies on the urine were not revealing.

A vaginal hysterectomy and posterior repair were done under spinal anesthesia by Dr. G. C. Cook on January 27, 1943. The ovaries were normal in size and the left one contained a thin-walled cyst, 1 cm. in diameter, which was ruptured at the time of operation and was found to possess a smooth lining and to be filled with a clear fluid. The adnexa were otherwise normal.

The patient had an uneventful postoperative course and was discharged on the 17th hospital day. A follow-up examination 11 months after operation showed her to be free from her previous symptoms. No palpable masses were present in the pelvis at this time.

Pathological Examination

The specimen consisted of the entire uterus, which measured 11 by 6 by 5 cm. in its greatest dimensions. The cervix was large and boggy and the vaginal surface was smooth, except for an area immediately adjacent to the external os where irregular areas of reddish brown discoloration were seen. The external surface of the body and fundus was smooth and glistening. The endometrial cavity was found to be filled with blood. Attached to the fundus on its posterior surface was an oval-shaped, firm nodule which was covered by endometrium and measured 2 cm. in diameter. It was well encapsulated and occupied a submucosal position. The endometrium covering the tumor and im-

mediately adjacent to it measured 1 mm. in thickness, while elsewhere it varied from 2 to 3 mm. The myometrium averaged 2 cm. in thickness and was without evident gross lesions. On sectioning, the tumor was found to be yellow and moderately firm; heavy, grayish white bands radiated throughout its substance.

Serial sections of the entire neoplasm revealed in every instance a well circumscribed and encapsulated tumor which occupied the submucosal position (Fig. 1). The myometrium immediately adjacent to the tumor was atrophic but otherwise presented no abnormalities (A in Fig. 1). A careful search was made for extracapsular tumor cells but none could be found.

The endometrium which covered the tumor, and that immediately adjacent to it, was thin and atrophic, and the longitudinal axes of the glands were parallel to the surface (B in Fig. 1). Elsewhere, the endometrium was hyperplastic and composed of numerous irregular glands which were situated in active interstitial tissue. The glands were thickened and were frequently composed of several layers of cells. In most instances the tumor was sharply demarcated from the remaining endometrium, although at several points considerable intermingling of tumor cells and endometrial stroma was noted.

The tumor was composed of groups of epithelial cells which were separated from each other by irregular bands of connective tissue. These bands radiated throughout its substance and frequently showed hyalinization. In many instances the parenchyma and stroma were so arranged as to form diffuse sheets of epithelial cells and not infrequently they presented a cylindromatous pattern (Figs. 2 and 3). A definite tendency toward rosette formation was clearly demonstrated in many areas (Fig. 4). The epithelial cells possessed large, darkly staining nuclei with scant cytoplasm. These cells were morphologically identical with granulosa cells and were more or less uniform in appearance. An occasional mitotic figure was seen. Varying degrees of luteinization were present in different areas, and clusters of cells showing extensive vacuolization were scattered throughout the neoplasm (Fig. 5).

At several points a sharp line of demarcation could not be drawn between the tumor proper and the endometrium. At these points the tumor cells were intimately associated with the mesodermal cells making up the endometrial stroma. These mesodermal cells appeared to possess embryonic properties, and differentiation into both epithelial and spindle cells could be seen. In many instances within the endometrium proper there were formed clusters of rosettes which were com-

posed of lutein-like cells, some of which displayed vacuolization (Fig. 6).

Laidlaw's method for the demonstration of reticulum was employed. The epithelial cells were found to be devoid of fibrils, and the cylindromatous pattern previously noted was now even more pronounced (Fig. 7). Spindle-shaped cells could be seen among the argyrophilic fibers, which communicated freely with one another.

Frozen sections stained with scharlach R revealed large quantities of sudanophilic fat, which occupied an intracellular position. Additional material examined with the polariscope was not doubly refractive and was probably neutral fat.

Discussion

The most frequent heterologous tumor occurring in the uterus is the so-called mixed mesodermal tumor. It is probable that these tumors originate from pluripotential mesodermal cells which differentiate into one or more structures ordinarily originating from the mesoderm. There exists at present considerable confusion regarding the exact criteria to be satisfied before a tumor can be placed in this group. This is evidenced by the fact that, in independent reviews appearing in 1941, Glass and Goldsmith [6] accepted from the literature 94 tumors as mixed mesodermal neoplasms of the uterus, while Lebowich and Ehrlich [4] would admit only 12. The latter authors, following the example of Läwen,[8] insisted on the presence of striated muscle in the tumor for it to be acceptable. Since these tumors represent a distinct pathological entity and follow a rather typical course clinically, it would appear unwise to exclude the majority of them on rather arbitrary histological criteria.

In rare instances, heterotopic tumors appear in the uterus which are identical morphologically with neoplasms occurring characteristically in organs quite remote from that structure. Schiller [9] described a tumor occurring in the uterus of a woman, 47 years old, which was morphologically identical with the ordinary ovarian dysgerminoma.

The case we have reported represents the first recorded instance of a neoplasm originating within the uterus which was morphologically identical with a granulosa cell tumor. The possibility of such an occurrence has, however, been suggested by Schiller, and others. Extraovarian granulosa cell tumors are extremely rare. Ragins and Frankel [10] have described a large intraligamentous granulosa cell tumor which was removed from a Negress, 37 years old, who presented no evidence of tumor in her ovaries. Voigt [11] has reported a retroperitoneal granulosa cell tumor which occurred in the absence of neoplastic disease in

the ovaries. Walthard and v. Werdt,[12] Klaften[13] and Fauvet[14] have each described retroperitoneal recurrences following the removal of granulosa cell tumors from the ovary. Schiller[15] is of the opinion that these tumors arose independently of the ovarian neoplasms and had their origin in mesodermal rests which had remained retroperitoneal and had not come in contact with the ovary. Clinical evidence in favor of this concept is found in the complete cures which have followed the removal of recurrent neoplastic tissue. Such cures are not obtained in other recurrent ovarian carcinomata.

Most investigators are now of the opinion that the granulosa cells are derived from the mesenchyme and not from the germinal epithelium, as has been the orthodox teaching for many years. Histogenetically, our tumor is best explained by assuming an origin from mesodermal cells that had retained their potentiality for producing granulosa cells in adult life. In this case, as in others, the stimulus for tumor formation remains unknown.

Summary

Heterologous mesodermal tumors occurring in the uterus are not extremely rare. They are usually of the mixed variety and are best explained histogenetically by assuming an origin from pluripotential mesodermal cells which have remained dormant and for some unknown reason assume neoplastic properties.

Occasionally, mesodermal tumors are found in the uterus which are identical with neoplasms originating characteristically in other situations. Such a tumor is the dysgerminoma of the uterus reported by Schiller.[19]

In this paper the first case of a neoplasm originating in the uterus, which was morphologically identical with a granulosa cell tumor of the ovary, has been reported. It is presented as evidence against the view which is prevalent among many morphologists that the granulosa cells arise from the celomic epithelium.

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DESCRIPTION OF PLATES

PLATE 10

FIG. 1. A section through the entire tumor, which includes the adjacent myometrium. (A) Myometrium. (B) Endometrium. That portion which covers the tumor is thin and atrophic. (C) Tumor. × 7.

FIG. 2. Large groups of epithelial cells are seen and in certain areas there is a tendency towards a cylindromatous arrangement. × 90.

FIG. 3. A higher magnification of an area seen in Figure 2. × 320.

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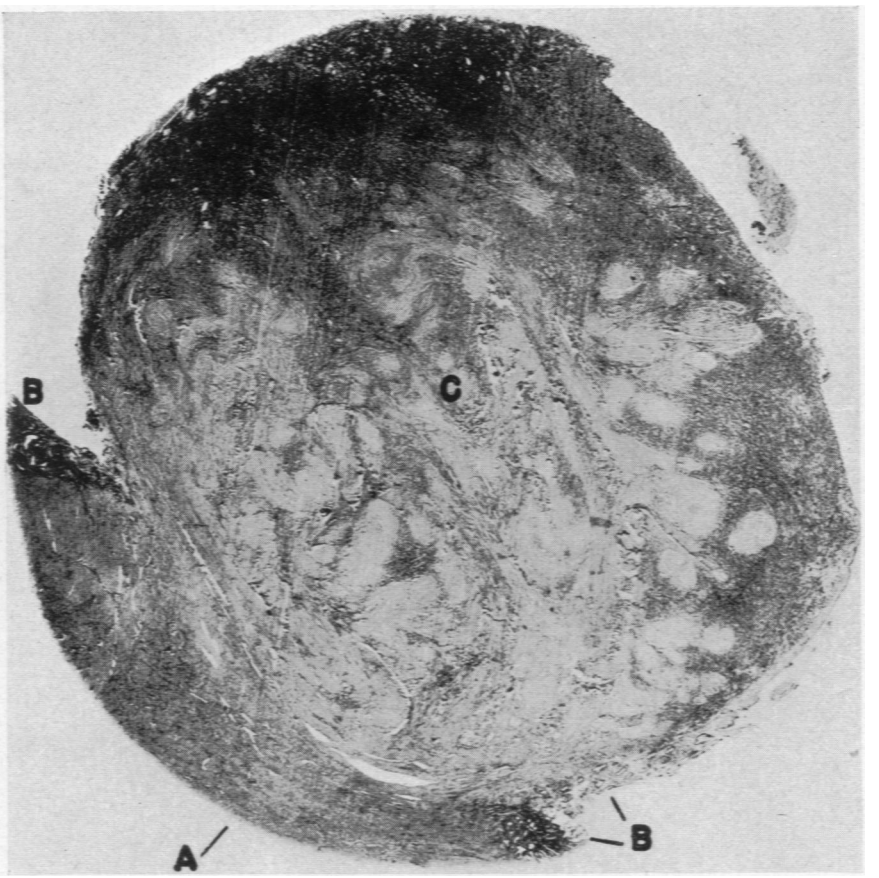

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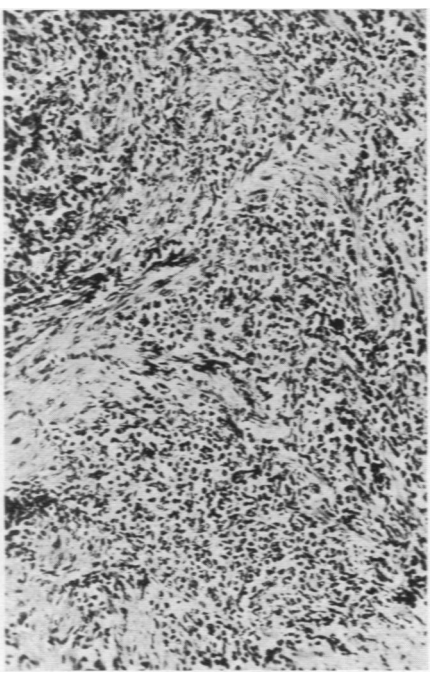

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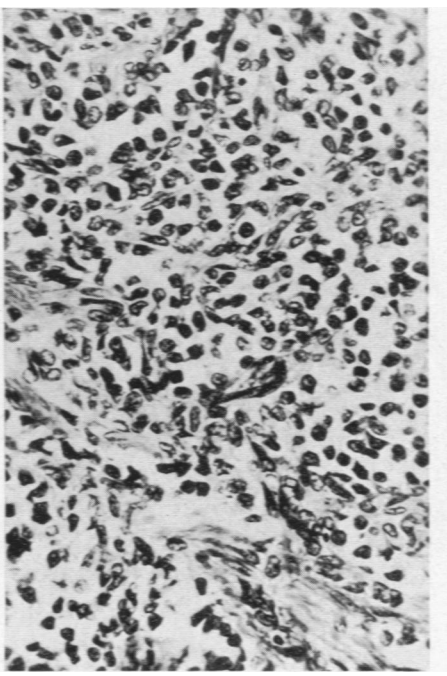

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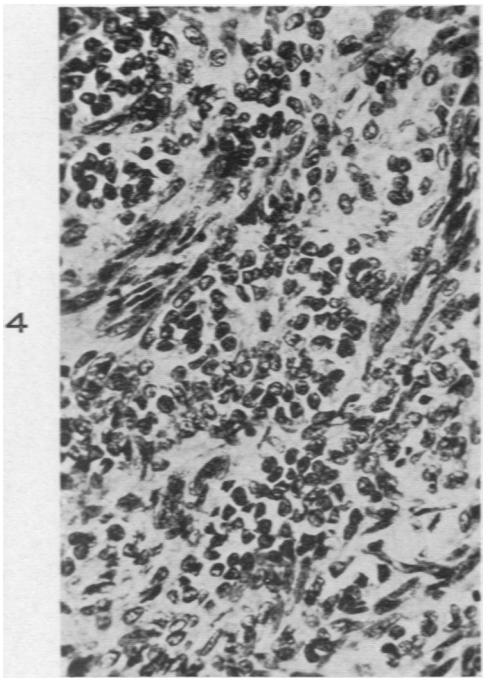
Plate 11

Fig. 4. A well formed rosette is seen in the center of the photograph. × 320.

Fig. 5. A group of epithelial cells, many of which contain neutral fat, are incompletely limited by dense fibrous tissue. Certain of the vacuolated cells show an alveolar grouping while others are scattered diffusely throughout the tumor. × 100.

Fig. 6. An area intimately associated with the endometrium. Mesenchymal cells here appear to be differentiating into both epithelial and spindle-shaped cells. The lutein-like cells are arranged in a characteristic grouping. × 90.

Fig. 7. Section stained for reticulum, showing the characteristic cylindromatous pattern and the absence of fibrils in the parenchyma. × 100.



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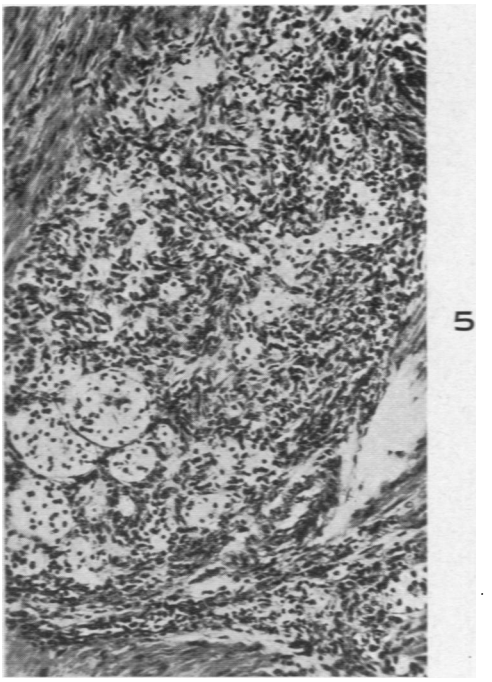

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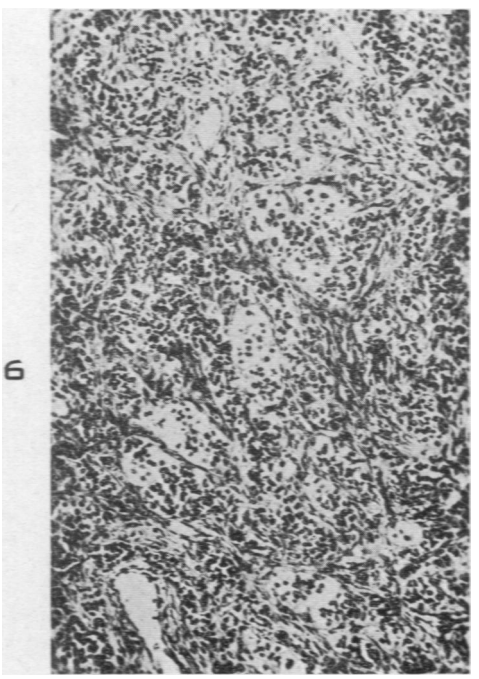

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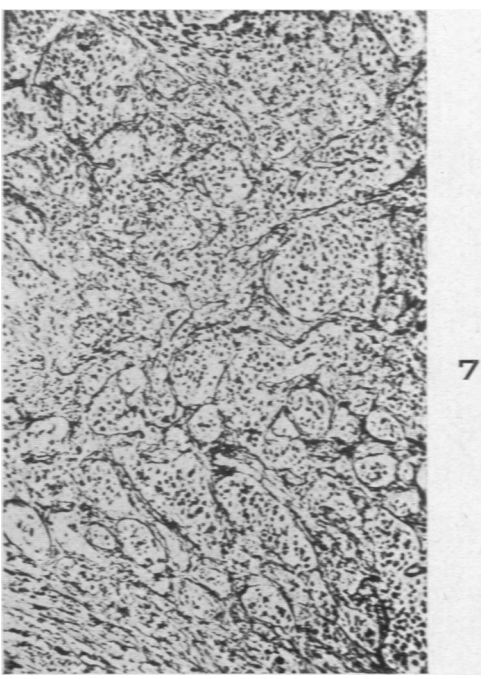

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