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PRIMARY GERM CELL TUMOR OF THE ANTERIOR MEDIASTINUM WITH FEATURES OF ENDODERMAL SINUS TUMOR

(*Mesoblastoma Vitellinum*)

By

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The anterior mediastinum and the pineal gland share the curious property of being the site of predilection for the development of the extragonadal germ cell tumors. Teratomas, embryonal carcinomas, chorioepitheliomas and seminomas have been described in these locations (*Friedman* (5), *Kounitz et al.* (7), *Oberman et al.* (10), *O'Gara et al.* (11). *Inada & Nakano* (8), *Lattes* (9)). In contrast to the adult testes however, most of the germ cell tumors in extragonadal location are benign. The reason for this difference and for the location of primordial germ cells in these organs is unknown. The study of this interesting group of neoplasms is impaired by their rarity, and justifies the reporting of single cases. In the ovary and in the testis, *Teilum* (15, 16) described germ cell neoplasms characterized by a mixture of undifferentiated neoplastic "mesoblastic cells" and irregular spaces, closely resembling the endodermal sinuses of Duval characteristic of the rat's placenta (*Duval* (4)). The author considered this type of neoplasm as an extraembryonic membrane tumor, morphologically distinct from the extremely varied group of the embryonal carcinomas. The following report of a case of anterior mediastinal primary germ cell tumor with endodermal sinus features is the first published documentation of such a tumor in the anterior mediastinum; the second of extragonadal origin. We are certain more cases will be recognized when the characteristic features of this neoplasm will become more widely known.

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CASE REPORT

A thirty-three year old Negro man was admitted to Michael Reese Hospital and Medical Center because of fatigue, weight loss, mild substernal pain and cough productive of black-stained sputum. His symptoms had initiated ten months earlier, and had become progressively more severe during the past four months. The family and personal history was non-contributory. On admission, physical examination disclosed no significant findings other than moderately enlarged left cervical and supraclavicular lymph nodes. Laboratory data were within normal range. A chest x-ray and tomogram revealed a large anterior mediastinal mass which displaced the trachea posterior. The clinical impression was that of a malignant lymphoma or a thymoma, although the possibility of a teratoma could not be entirely ruled out. Biopsy of the supraclavicular lymph nodes revealed only non-specific lymphoid hyperplasia.

On the seventh hospital day mediastinoscopy revealed a large tumor mass which occupied the anterior mediastinum, surrounded the large vessels and extended into the right pleural space. The mass was of deep gray-purple color and was extensively necrotic. It could be only partially resected in view of its relationships with the superior vena cava and the innominate vein.

Following surgery, the patient made an uneventful recovery, although cytological examination of the sputum revealed the presence of malignant cells, indicating extension of the tumor to the tracheo-bronchial wall. He was discharged two weeks later and followed in the out-patient department. He received 12,210 r. to the anterior mediastinum in twenty-seven treatments over a period of thirty-eight days. He appeared to tolerate the treatment well; however, two months following his first admission he noticed bilateral subcutaneous masses in the anterior chest wall which were considered as metastases. For these, additional 5000 r. were administered by means of Co. 60 radiation. In spite of therapy he became progressively weaker, had repeated hemoptysis and became markedly anemic. The second admission was four months following discovery of the tumor. At this time there were left supraclavicular and posterior cervical lymphadenopathy and left pleural effusion. A test for urinary gonadotropin was negative. The patient received Cytoxan, Nitrogen mustard and Tetracycline intrapleurally. Despite all therapeutic efforts he declined rapidly and expired in marked respiratory distress five months after the initial diagnosis had been made.

Pathology

The surgically removed tumor consisted of a partially encapsulated, gray-purple mass which measured 11×8×6 cm, and weighed 208 gm. On section, it was gray-purple in color, soft, centrally necrotic and hemorrhagic.

Microscopically, the tumor was composed of several cell types. The main portion was formed by solid masses of large cells with clear cytoplasm and round to pleomorphic nuclei with delicate chromatin and prominent nucleoli (Fig. 1). Intermingled were areas of stellate cells connected by delicate projections and forming a loose network with wide meshes (Fig. 2). Imperceptibly merging with these areas of undifferentiated cells were irregular spaces lined by low cuboidal or

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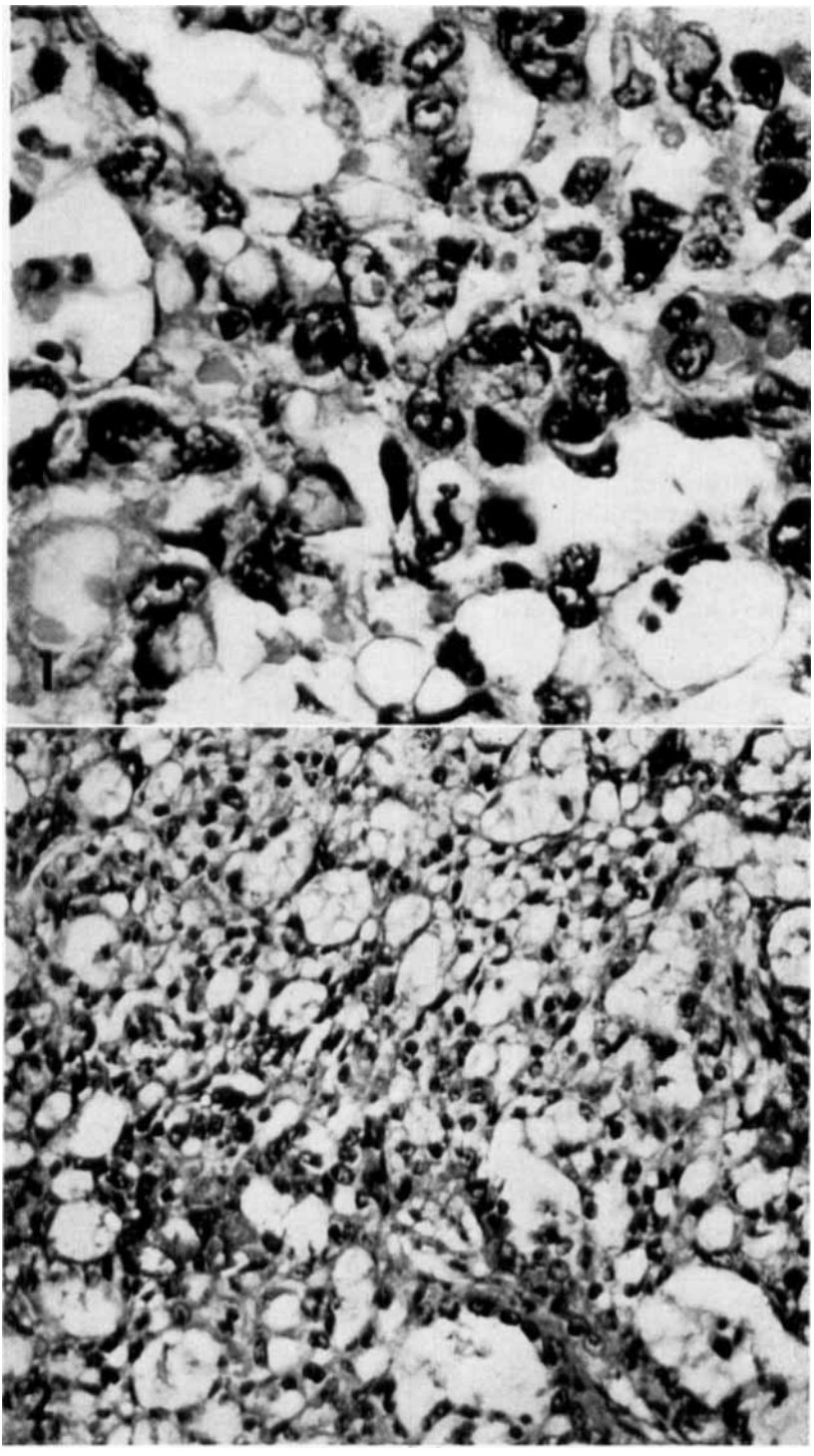
Figs. 1–2.

Fig. 1. The tumor is composed of solid nests of large, undifferentiated cells with clear cytoplasm. Some of the cells have large cytoplasmic vacuoles. Note the cystic spaces lined by flattened cells. (H.E. × 613).

Fig. 2. Areas showing clumps of markedly vacuolated cells forming delicate cobweb-like structures with developed microcysts. (H.E. × 200).



flattened cells with large round or indented hyperchromatic nuclei and scanty cytoplasm. The cavities appeared to communicate with each other, forming an intricate system of irregular channels in which papillary structures projected (Fig. 3). The papillae were covered by a single layer of epithelial-like cells, supported by delicate connective tissue containing thin-walled blood vessels. On cross section, these papillary structures appeared as peculiar "glomerularlike" formations with a single capillary in the center, covered by a mantle of cylindric cells of epithelial character (Fig. 4). These structures (Fig. 5) have been interpreted as invaginated yolk sac endoderm accompanying the vessels of the extra-embryonic mesenchyme (15, 16). In the cytoplasm of both the flattened cells and in the epithelial-like cells there were eosinophilic, strongly PAS-positive droplets. In addition extracellular accumulations of such hyaline globules were often present (Fig. 5).

At the periphery, the tumor mass was partially surrounded by dense collagen, in which residual thymic tissue was present (Fig. 6). Within the tumor mass were small lymphoid foci, possibly representing residual lymphatic tissue of the thymus.

As the cells of the sputum appeared quite unusual, a description of these may be of interest. The cells appeared mostly single or in pairs. Some of the cells had large cytoplasmic vacuoles, large nuclei which appeared round or oval with distinct nuclear membranes, and finely dispersed chromatin. Some were hyperchromatic, lobulated and irregular in outline with chromatin clumping (Fig. 7). The nucleoli varied in size and shape.

At autopsy the original surgical site was entirely obliterated by tumor regrowth and the anterior mediastinum beneath the sternum was occupied by a large, yellowish-gray tumor mass with multiple areas of hemorrhagic necrosis and an outer layer of intense reddish-brown, soft tumor tissue extending to the entire left parietal and visceral pleura and lung. The thymus gland was not recognized as such. Hemorrhagic and sero-fibrinous fluid filled most of the left pleural space, with subsequent compression of the lung. On the right side the pleural lining and cavities were free of tumor; however, there was presence of confluent bronchopneumonia and multiple thromboemboli within the peripheral vessels of the lungs.

In addition to local extension, the tumor had metastasized widely throughout the body. Almost all of the thoracic lymph nodes were involved bilaterally, including the mediastinal, hilar and peribronchial lymph nodes, as well as the supraclavicular and paraaortic lymph

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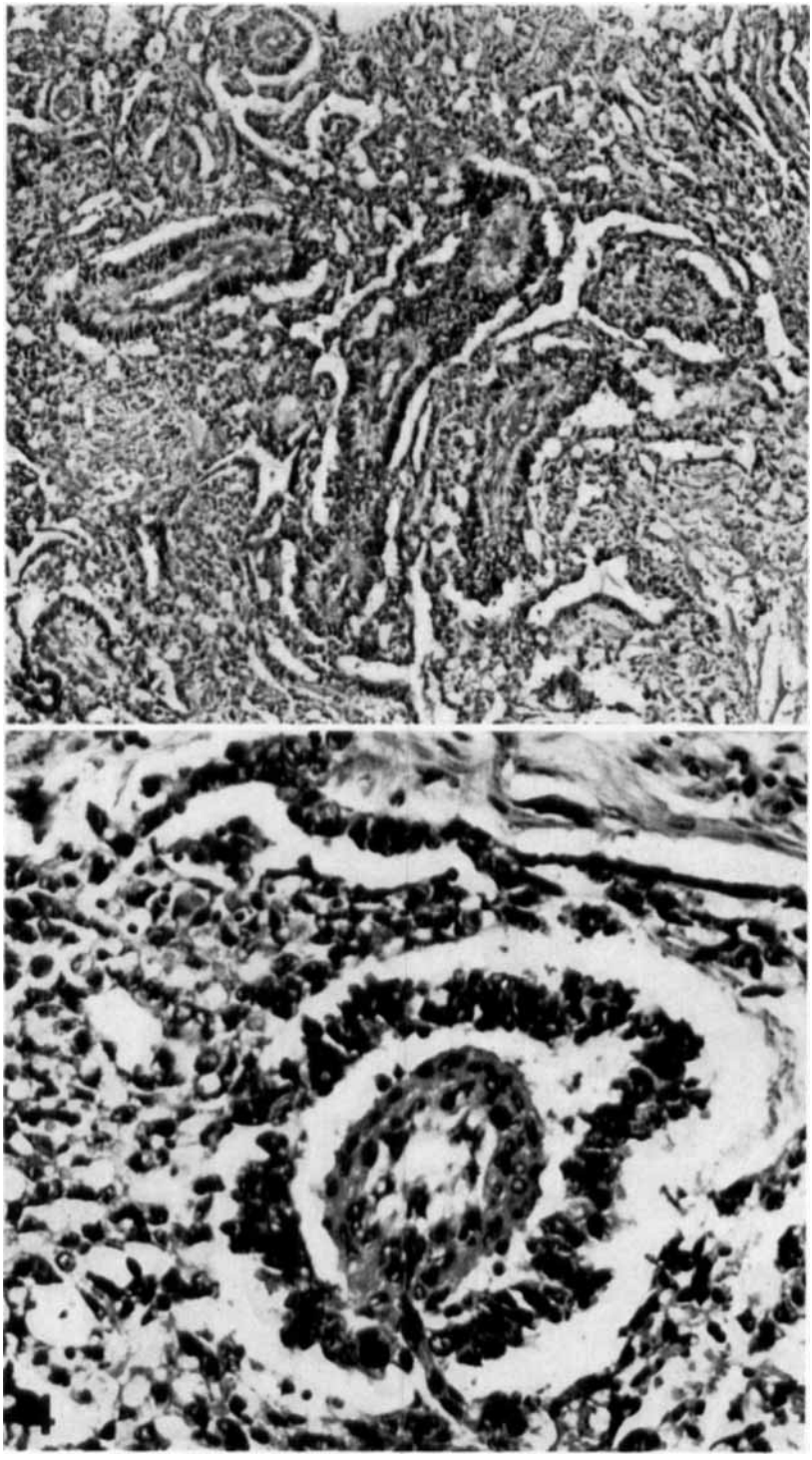
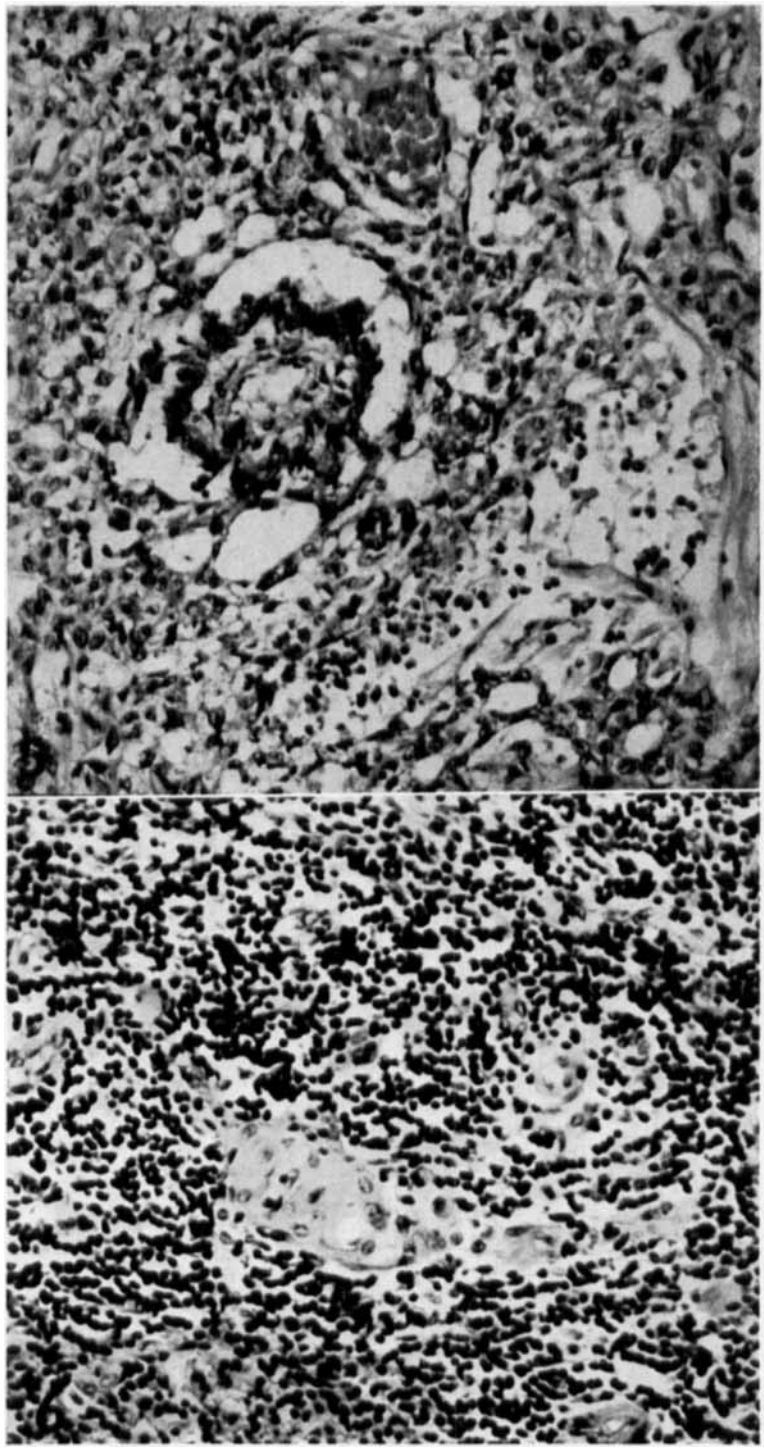
Figs. 3–4.

Fig. 3. Systems of irregular channels lined by low cuboidal epithelium. Note the papillary formations with a blood vessel in their centre. In cross section such structures vaguely resemble immature renal glomeruli. (H.E. × 90).

Fig. 4. Endodermal sinus structure with perivascular mantling of cells. (H.E.×240).





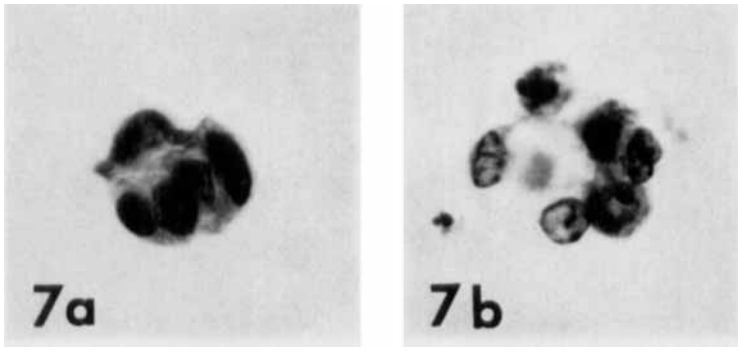


Fig. 7.
(a and b): Tumor cells in the sputum. Note in *a* the large oval shaped hyperchromatic nuclei and the scanty cytoplasms. In *b* the cell on the left has a large cytoplasmic vacuole; the remaining cells have round or lobulated nuclei, clumping of the chromatin and nucleoli of varying size. (Papanicolaou × 575).

nodes. Metastases were present in the liver and in the skin of the left anterior chest wall. Careful attention was given to the examination of the testes. No tumor tissue was seen grossly or microscopically in any of the multiple sections examined by the method of serial blocks. Further, there were no areas of scarring in the testes. A striking feature was the widespread atrophy of the germinal epithelium and hyaline thickening of the tubular basement membrane. The tubules were lined by Sertoli cells and few scattered spermatogonia. The interstitial cells were well preserved and did not appear increased in number (Fig. 8).

Microscopic examination of the tumor revealed essentially the same characteristic features seen in the surgical specimen (Fig. 9). In addition, many of the metastatic masses showed a more undifferentiated pattern. In some of the sections of the recurrent mediastinal tumor there were large cells with strongly eosinophilic cytoplasm and large hyperchromatic nuclei resembling syncytiotrophoblastic cells.

DISCUSSION

As illustrated in the Figs. 1 through 5 and Fig. 9, the anterior mediastinal neoplasm reflects the histologic features of the endodermal sinus tumor as described by *Teilum* (15, 16) in the ovary and testis. These

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Figs. 5–6.

Fig. 5. Area of the mediastinal tumor showing the characteristic endoderm sinus structure representing yolk sac endoderm that expands and dissects around the vessels of the extraembryonic mesenchyme. The structure is surrounded by a loose vacuolated network of stellate mesodermal cells and small cystic spaces showing focal accumulations of PAS-positive hyaline globules. (H.E. × 200).

Fig. 6. Well preserved thymic tissue at the periphery of the anterior mediastinal tumor. Note the Hassal's corpuscle. (H.E. × 240).

Fig. 8.
Representative section of the testis. The tubules are lined by Sertoli cells and isolated spermatogonia. Note the marked thickening of the tubular basement membranes. (H.D. × 60).

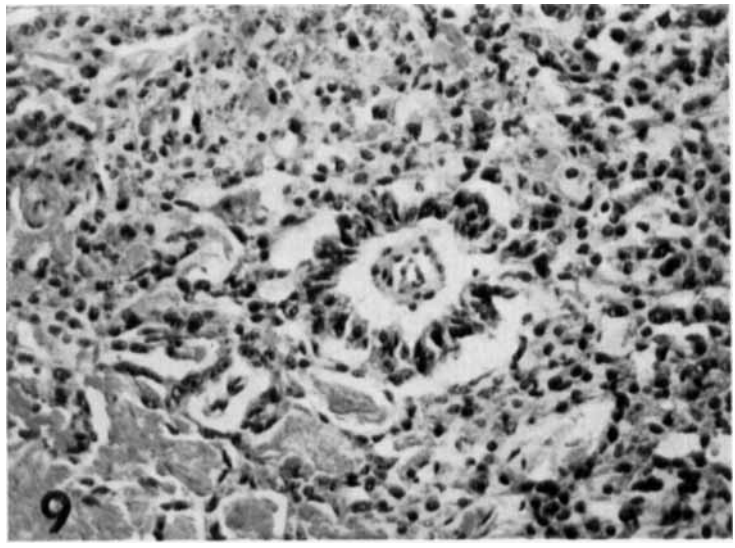

Fig. 9.
Pulmonary metastasis. The tumor although generally more undifferentiated in the metastases reveals focally the typical endodermal sinus pattern. (H.D. × 150).

are: (a) areas formed by stellate mesodermal cells forming a loose vacuolated network delineating irregular spaces lined by flattened, endothelial-like cells, and often containing foci of active hemopoiesis; (b) endodermal sinus structures characterized by perivascular arrangement of cylindric epithelium which in cross section vaguely resemble immature glomeruli. They are surrounded by cystic spaces lined by a single layer of flattened mesothelial-like cells with prominent nuclei. In longitudinal section they appear as a complete labyrinth resembling the endodermal sinuses of the rodent placenta; (c) compact masses of undifferentiated cells similar to the undifferentiated cells of the developing embryo; and (d) cystic structures lined either by flat mesothelial-like cells or by low cuboidal epithelial-like cells. These cysts are considered analogue to the yolk sac of the early embryo.

The proportion of the various patterns vary considerably, not only in different tumors but also in different areas of the same tumor. In the present case the features mentioned in (d) were not seen. However, there was a striking resemblance to the ovarian and testicular tumors described by *Teilum* (15, 16) as endodermal sinus tumor, with the testicular neoplasms of infant testis reported by *Huntington et al.* (6) and with the sacrococcygeal teratoma of *Raghunatha et al.* (12), also considered examples of endodermal sinus tumors.

In Teilum's opinion this tumor represents the differentiation of entirely undifferentiated neoplastic embryonal cells (15, 16) into extraembryonic membrane structures such as the mesoblast and yolk sac endoderm. Teilum's interpretation of the histogenesis of these neoplasms was based on comparative studies, which among other things showed a striking resemblance of the perivascular sinusoid structures in the tumor with the embryologically well-defined endodermal sinus structures, which are prominent in the rat placenta. In both instances these formations represent diverticula of yolk sac endoderm, that expand and dissect around the vessels of the extraembryonic mesenchyme. While this comparison is valid not only in regard to the general appearance in cross and longitudinal sections, but also to the type of lining cells, it would not imply a specific capacity of the tumor to reproduce phases of placentation in the rodent (17).

The ovarian tumors show a far more uniform histologic pattern than their testicular counterparts in adults, which usually reveal great variations of immature embryonic tissues. The term "embryonal carcinoma" has been a subject of criticism since it lacks clarity and leads often to confusion by its ambivalent use. For practical use the term may be retained to designate these complex germ cell tumors of the adult testis, which comprise a fairly homogenous *clinical* group. However, it is not sufficient basis for histologic characterization and recognition of the ovarian counterparts and similar tumors in the infant testis or extragonadal positions (16).

In our case, the pattern of endodermal sinus tumor was striking in

the resected tumor but only found locally in the recurrent tumor and its metastases (Fig. 9). Clinically, the neoplasm as the embryonal carcinoma of the adult testis affect the same age group and is resistant to radiation or chemotherapy. In contrast to the behaviour of this type of neoplasm in children all cases of endodermal sinus tumor in the adult have a malignant course regardless of treatment.

It is well known that gonadal malignant teratomas, "embryonal carcinomas" and choriocarcinomas may metastasize solely to the mediastinum. In this case, however, serial blocks of the testis failed to show any tumor or scar. In addition thymic tissue was identified at the periphery of the neoplastic mass (Fig. 6). It is then reasonable to assume that this tumor arose in the thymus gland or in its proximity. There is no agreement as to the factors which lead to the development of gonadal and extragonadal teratomas and "embryonal carcinomas". *Willis* (18), *Collins & Pugh* (2) deny their origin from germ cells and believe that they arise from foci of plastic pluripotential embryonic tissue, which have escaped from the influence of the primary organizer during fetal life. Most authors, however, believe in their origin from germ cells through different stages of development (*Friedman* (5)), *Dixon & Moore* (3), *Teilum* (15, 16), *Bhargava & Reddy* (1). *Schlumberger's* (13) interpretation that the mediastinal germ cell neoplasms arise from the third branchial pouch, the anlage of the thymus, seems unlikely. It is now generally accepted that the germ cell neoplasms in this region are derived from germ cells which have been misplaced during ontogeny and that during their passage from the yolk sac endoderm they have travelled through the retroperitoneum to the mediastinum instead of the gonadal ridges (*Teilum* (17)). Of interest was the presence of a marked degree of atrophy of the germinal epithelium and the thickening of the basement membranes of the tubules of the testis. No explanation is readily available for this process; it may have been the result of inanition and chemotherapy although the latter appears unlikely in view of the findings of *Oberman & Libcke* (10). Three patients in their series of mediastinal malignant germ cell tumors had similar testicular findings. These authors do not state which one of the patients of their series had testicular tubular atrophy but only one was treated with nitrogen mustard, the others received only x-ray therapy or were surgically treated. No explanation has been offered to clarify the striking preference of the malignant germinal tumor for the male, while the incidence of the benign counterpart is approximately the same in both sexes. Similar contrasting ratios of malignant and benign teratomatous tumors in the two sexes are seen also in the gonadal tumors. Here the suggestion has been presented ((3) p. 53 and (14) p. 226) that the environment in the female gonads predisposes germ cell neoplasms to differentiation, whereas the male environment fosters undifferentiated growth. This hypothesis could be extended to extragonadal germ cell tumors. It is conceivable that in the female the same

genetic material has greater potency to differentiation, possibly because of a more suitable endocrine environment. In this respect it is of interest that the endodermal sinus tumors—which in *Teilum*'s (15, 16) view are extra-embryonic, and, in fact, endodermal derivatives from germ cells—are rare in the adult testis, but common in the testis of the young child and in the ovary.

SUMMARY

The first case of mediastinal germ cell tumor with endodermal sinus features in a thirty-three year old Negro male is reported. The neoplasm exhibited the predominant pattern of communicating cavities, lined by cuboidal or flattened cells and papillary structures as described in the ovary originally by *Teilum*. The tumor was rapidly fatal and metastasized widely.

The specific histological features of endodermal sinus tumors in this and other regions will enable their proper identification and distinction from other types of neoplasm.

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