Classification of Tumors of the Ovary: Developmental and Ultrastructural Considerations

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ABSTRACT

The classification of ovarian tumors presents a difficult problem because of the great variety of tumor types that can occur. The complex structure of the normal ovary and the diversity of cell types present at different stages of development contribute to this difficulty. Developmental and ultrastructural studies have helped to clarify the problem by indicating specific cell types that correspond directly with the major tumor categories. Tumors may thus be grouped as being of epithelial, germ cell or sex cord stromal origin. The ultrastructural features of tumors in the different categories indicate common characteristics shared with corresponding cell types in the developing ovary. The findings clearly support a histogenetic approach in the classification of ovarian tumors.

Introduction

The diversity in histologic appearance and clinical behavior of tumors of the ovary presents a particularly difficult problem to pathologist and clinician alike. For the pathologist, the number of different categories of ovarian tumors is in itself an imposing challenge. In addition, there are so many sub-types in the various categories that only a thorough understanding of the classification of tumors of the ovary will enable a correct interpretation and proper designation in evaluating such cases. For the clinician involved in the management of patients with ovarian tumors, the problem is further complicated. Not only do the tumors have different appearances, but they also behave in entirely different ways in their clinical presentation, laboratory findings, response to various forms of treatment and eventual outcome. It is therefore critical that the pathologist be able to convey to the clinician an appropriate and accurate diagnosis in cases of ovarian neoplasia.

The complexity of the problem is underscored by the multiplicity of approaches to the analysis of ovarian tumors that have existed over the years. The most successful of these have been based on histogenetic considerations. Utilizing such an analysis, the World Health Organization has proposed a standardized classification and nomenclature of ovarian tumors. This classification is reviewed in a recent paper to which the
reader is referred. Since the present author is in essential agreement with the WHO classification, the purpose of this report is not to present a new classification, but rather to add support to the histogenetic approach, using data derived from developmental and ultrastructural studies.

Development of the Ovary

Implicit in a histogenetic approach to tumor classification is an understanding of the different normal cell types involved. The ovary is a complex structure participating in two major functions which are interrelated but distinct: reproduction and hormone secretion. These functions require several cell types, i.e., germ cells, supporting cells, hormone secreting cells.\textsuperscript{19}

The development of these different cell types within a single organ requires intricate coordination and interaction. Much of this complex developmental process takes place in the fetal ovary.\textsuperscript{56} Consequently, understanding of ovarian histogenesis entails special consideration of fetal stages of development. Table I indicates the principal cell types present in the fetal ovary. These are the surface epithelial cells, germ cells (primitive germ cells, oogonia, oocytes), granulosa cells and stromal cells.

The surface epithelium of the fetal ovary represents an extension of the coelomic epithelium (mesothelium) over the developing gonad. The gonads initially develop as outpouchings into the coelomic cavity in the region of the genital ridge. Immediately adjacent to the forming gonads, the coelomic epithelium invaginates and extends caudally to give rise to the Müllerian ducts, the source of the major part of the female genital tract. A special feature of the epithelium overlying the fetal ovary is that it undergoes extensive proliferation during the second trimester,\textsuperscript{20} then reverts to a single layer as is present in the adult.\textsuperscript{43} The proliferation occurs during the formation of cortical sex cords which contain germ cells and granulosa cells. The surface epithelium contributes to the formation of the granulosa cells,\textsuperscript{16} some of which are also derived from the rete ovarii.\textsuperscript{8}

The germ cells originate extragonadally in the yolk sac endoderm, then migrate to the developing gonad during the second month of gestation.\textsuperscript{58} Initially referred to as primitive germ cells, these cells become closely associated with adjacent granulosa cells on arrival in the gonad and undergo active proliferation, TABLE I

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Specific Name</th>
<th>Origin</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Epithelial</td>
<td>Surface epithelium</td>
<td>Coelomic epithelium</td>
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<td>Germ cells</td>
<td>Primitive germ cells</td>
<td>Yolk sac</td>
<td>Large round to oval ameboid cells. Round cells in active mitosis, in clusters.</td>
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<tr>
<td></td>
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<td></td>
<td>Round cells in meiosis, become incorporated in follicles.</td>
</tr>
<tr>
<td></td>
<td>Oocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supporting</td>
<td>Granulosa cells</td>
<td>Surface epithelium/</td>
<td>Elongated cells at edge of follicle. Undifferentiated stromal cells.</td>
</tr>
<tr>
<td>Stromal cells</td>
<td>Theca interna</td>
<td>Reto ovarii/Mesenchyme(?)</td>
<td>Large oval cells with abundant cytoplasm.</td>
</tr>
<tr>
<td></td>
<td>Theca externa</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interstitial cells</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE I

Cell Types in Developing Ovary

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<td></td>
</tr>
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at which time they are called oogonia. This mitotic phase is followed by a meiotic phase which begins at the end of the third month. The cells in meiosis are then referred to as oocytes.

Until mid-gestation, the germ cells and granulosa cells are arranged in cortical aggregates without evident organization. Toward the end of the fifth month the first follicles begin to appear, starting in the innermost region of the cortex. The process of folliculogenesis, involving the surrounding of individual oocytes by a unilaminar envelope of flattened, elongated granulosa cells, continues over the next several months. By the early neonatal period, all of the oocytes present have become incorporated in follicles. Many of the original population of oocytes in the fetal ovary degenerate prior to becoming incorporated in follicles, with only a limited number surviving the earlier prefollicular stages.

The final major tissue component of the developing ovary, the mesenchyme, remains largely undifferentiated during the fetal period. With the beginning of follicle growth in the latter part of gestation, mesenchymal or stromal cells become associated with the follicles. These cells, located outside the basement membrane enclosing the granulosa cells and oocyte, constitute the theca interna. The stromal elements adjacent to but not associated with the follicle are referred to as the theca externa. The theca interna and granulosa cells are the cellular elements principally responsible for production of sex hormones. This activity becomes most evident in the reproductive years when, following ovulation, the two cell types undergo luteinization, a process whereby accumulation of organelles associated with steroid hormone production results in great cellular enlargement. The hormones produced are of estrogenic and progesterational type. Hormone secretion also takes place prior to luteinization and in the immature ovary.

Another cell type of apparent mesenchymal origin is that associated with androgen production. Interstitial cells, hilar cells, Leydig cells are names given to the ovarian stromal cells which are homologous to the Leydig cells of the testis. The latter are clearly derived from mesenchyme. Interstitial cells appear in the fetal ovary as early as the end of the third month of gestation. Their capacity for and involvement in endocrine activity at this time are unclear. In the mature ovary, it appears that such cells are involved in androgen production.

### Tumors of the Ovary

The developmental analysis described previously indicates the following principal cell types: epithelial cells, germ cells, granulosa cells and mesenchymal (stromal) cells. As indicated in table II, ovarian tumors can be grouped in a corresponding manner, i.e., epithelial tumors, germ cell tumors and sex cord stromal tumors. The last category represents a combination of tumors derived from granulosa cells and stromal cells. The

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Tumor Type</th>
<th>Sub-Tyeps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelium</td>
<td>Epithelial</td>
<td>Serous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mucinous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrioid</td>
</tr>
<tr>
<td>Germ cell</td>
<td>Germ cell</td>
<td>Brenner tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mixed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Undifferentiated</td>
</tr>
<tr>
<td>Granulosa cell</td>
<td>Sex cord</td>
<td>Granulosa cell tumor</td>
</tr>
<tr>
<td>Stromal cell</td>
<td>Stromal</td>
<td>Thecoma-fibroma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sertoli-Leydig cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gynandroblastoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lipid cell tumors</td>
</tr>
</tbody>
</table>
frequent combination of these cell types within a single tumor and their common involvement in hormone production support such a grouping.

Epithelial tumors are the most frequent among both benign and malignant ovarian neoplasms. With some exceptions, most of the sub-types are cystic, have benign, intermediate and malignant forms, and are not associated with endocrine changes. They differ greatly in their malignant potential and manner of therapy. However, all share origin from surface epithelium. Several previous reports\textsuperscript{35,52} have pointed out the similarity of the cellular components of various sub-types to cells lining structures derived from the Mullerian ducts, e.g., serous-tubal, mucinous-endocervical and endometrioid-endometrial. Evidently, formation of the Mullerian duct lining from epithelium adjacent to the ovarian surface epithelium provides the latter with the same multipotential capacity for differentiation conferred on the Mullerian ducts. Similarly, the proliferative capacity of the ovarian epithelium associated with tumor formation may relate to its earlier developmental ability to proliferate.

Germ cell tumors include those derived directly from germ cells, dysgerminomas and those that are indirectly of germ cell origin. In the latter group are tumors with differentiation in an extra-embryonic direction—endodermal sinus tumor, choriocarcinoma; those with primitive embryonic differentiation—embryonal carcinoma, polyembryoma; and those with more advanced embryonic differentiation—teratomas. Included in the last group are some highly specialized forms showing specific patterns of differentiation—carcinoid tumors, struma ovarii. Tumors in the germ cell category exhibit great variation in clinical presentation, gross appearance, microscopic findings, prognosis and response to therapy. They share a common occurrence in the young age group and as a rule are not associated with endocrine abnormalities. Almost identical tumor types are found in the testis, where the special patterns of differentiation from germ cells have been classified in a similar manner.\textsuperscript{11,55} Interestingly, clinical behavior and frequency of occurrence may be quite different when ovarian and testicular tumors of corresponding cell type are compared.\textsuperscript{12}

Tumors of sex cord stromal type are generally solid and characteristically produce endocrine symptoms as a result of abnormal, excessive steroid hormone production. The symptoms may be related to estrogen secretion, as frequently occurs in the granulosa cell and theca cell tumors, or androgen secretion, as is generally associated with the lipid cell and Sertoli-Leydig cell tumors. Included among the lipid cell tumors are those derived from interstitial or hilar cells and others whose origin is not clear but may be from ectopic adrenocortical tissue. The occurrence of tumors in the ovary composed of Sertoli and Leydig cells is not surprising, since the ovary and testis both begin from a similar undifferentiated gonadal anlage.\textsuperscript{19} The cells of the ovary apparently retain the capacity of the primitive gonad to undergo Sertoli cell and Leydig cell differentiation. Also noteworthy in this regard is that the various tumors in the sex cord stromal group are potentially capable of producing a variety of sex steroids, a reflection of the interaction and differentiative capacity of the gonadal cell types involved in endocrine function. Thus, for example, granulosa cell tumors may be virilizing and Sertoli cell tumors may secrete estrogens. Furthermore, combinations of ovarian and testicular cell types may occur, as in the gynandroblastoma.

Ultrastructure of Ovarian Tumors

The clarification of ovarian histogenesis based on analysis of differentia-
Ultrastructure of Ovarian Tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Nucleus</th>
<th>Cytoplasm</th>
<th>Cell Membranes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial</td>
<td>Large, irregular with infoldings, marginated and coarse chromatin.</td>
<td>Abundant ribosomes, rough e.r., branched elongated mitochondria with transverse cristae, prominent Golgi.</td>
<td>Prominent junctional complexes, long irregular microvilli.</td>
</tr>
<tr>
<td>Germ cell</td>
<td>Large, round to oval, even chromatin pattern, large nucleoli, often multiple.</td>
<td>Scant organelles, rounded mitochondria with eccentric cristae.</td>
<td>Smooth, rare loose attachment zones.</td>
</tr>
<tr>
<td>Sex cord stromal</td>
<td>Eccentric, round, sl. chromatin margination, large single nucleolus.</td>
<td>Abundant smooth e.r., large mitochondria with villiform tubular cristae, prominent Golgi, lipid droplets</td>
<td>Scattered microvilli, numerous attachment zones, occasional desmosomes, gap junctions (?).</td>
</tr>
</tbody>
</table>

Correlation of information derived from these two sources, electron microscopic studies of normal ovarian development and of ovarian tumors, provides the basis for the material summarized in table III. Ultrastructural characteristics of epithelial tumors vary somewhat depending on the result of electron microscopic studies. Similarly, classification of ovarian tumors utilizing the histogenetic approach owes a great deal to ultrastructural studies. Correlation of information derived from

Figure 1. Electron micrograph, mucinous cystadenocarcinoma of ovary. Note irregular nuclear configuration and numerous flocculent deposits in cytoplasm. The deposits represent mucin (x 6,200).
on the type. For instance, serous tumors may contain apical secretory granules, mucinous tumors (figure 1) aggregates of mucinous material, and clear cell tumors abundant glycogen, while endometrioid carcinomas show large coiled nucleoli resembling normal endometrial cells. However, the basic characteristics of epithelial cells are evident in all of the different tumors (figure 2) and they can thereby be distinguished from the other major categories. Ultrastructural studies of Brenner tumors have supported the epithelial origin of these neoplasms. It has also been noted that the electron microscopic appearance of certain of the surface epithelial tumors bears a striking resemblance to surface epithelial cells in the fetal ovary.

The description of germ cell tumor ultrastructure refers only to those derived directly from germ cells, the dysgerminomas. These tumors faithfully reproduce the ultrastructural features of early germ cells (primitive germ cells, oogonia). Particularly noteworthy are the homogeneous distribution of chromatin, the large, often multiple nucleoli and the paucity of organelles in the cytoplasm giving the latter a rather watery appearance (figure 3). The ultrastructural characteristics of other germ cell tumors will depend on the type. A particular place for the use of electron microscopy is in the diagnosis of carcinoid tumors, which can be identified by the presence of neurosecretory granules.

Sex cord stromal tumors frequently show cytologic features associated with

![Figure 2. Papillary serous cystadenocarcinoma, with abundant microvilli and junctional complexes characteristic of epithelial cells (x 13,500).](image-url)
production of steroid hormones (figure 4). Such findings as proliferation of smooth endoplasmic reticulum, presence of large mitochondria and accumulation of lipid droplets have been noted in granulosa cell tumors,\textsuperscript{6,17,37,44,57} thecomas,\textsuperscript{2} Sertoli-Leydig cell tumors\textsuperscript{4,28,29,39,49} and lipid cell tumors.\textsuperscript{27,31,38} These features are characteristic of steroid secreting cells in the adult and developing ovary.\textsuperscript{19} In addition, steroid secreting cells have varying kinds of attachment zones on their surfaces and it is likely that gap junctions, which are prominent between normal steroid producing cells,\textsuperscript{1} would also be present on the cell surface of corresponding neoplasms.

Although this discussion has dealt only with primary ovarian neoplasms, it should be noted that electron microscopy might also be useful in identifying metastatic tumors to the ovary on the basis of specific cellular characteristics.\textsuperscript{53} In addition, some of the rare primary tumors not included in the major categories, such as gonadoblastoma,\textsuperscript{5,15} may show special ultrastructural features.

**Summary**

The histogenetic approach to the classification of ovarian tumors is supported and clarified by data derived from developmental and ultrastructural studies. Ovarian tumors can generally be categorized as arising from epithelial cells, germ cells or cells of sex cord-stromal origin. These tumor groups correspond directly with the principal cell types in the developing ovary: surface epithelial cells, germ cells, granulosa cells and mesenchymal cells. Electron microscopic evaluation of ovarian tumors has demonstrated that special ultrastructural features characterize the tumors in the different categories. The ultrastructural observations correlate closely with

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**Figure 3. Germ cell tumor of seminoma-dysgerminoma type.** Characteristic features are large, irregular nucleolus, evenly distributed chromatin and paucity of cytoplasmic organelles (x 12,500).
similar studies in the developing ovary, reinforcing the histogenetic approach. Thorough understanding of the developmental and ultrastructural basis for the histogenetic classification will greatly enhance the ability of the pathologist to evaluate the nature and potential behavior of ovarian neoplasms.

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