Ovarian tumors and tumor-like lesions in the first three decades

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Abstract

The relative frequency of ovarian tumors and tumor-like lesions that occur in young females (defined in this article as up to 30 years of age) differs considerably from that seen in older patients. The spectrum of lesions encountered is reviewed, with emphasis on those disproportionately seen in younger patients, particularly primitive germ cell tumors, certain tumors in the sex cord-stromal family, the distinctive tumor known as small cell carcinoma of hypercalcemic type, and selected tumor-like lesions. Comments are made initially on the relative frequency of the various well-known categories of ovarian neoplasia in the first three decades, compared to females overall, and differences within the first three decades are noted. Some of the more noteworthy of these include the occurrence of follicular cysts in neonates due to in-utero maternal stimulation, and the often large size of these lesions, with sometimes dramatic clinical manifestations; the relative rarity of the commonest germ cell tumor of the ovary, the dermoid cyst, in the very early years of life; the peak incidence of all primitive germ cell tumors in the mid to late teens and early 20s; the peak of small cell carcinoma of hypercalcemic type in the early 20s; the preponderance for the juvenile granulosa cell tumor to occur in the first two decades and for one distinctive form of Sertoli-Leydig cell tumor, the retiform variant, to peak at about 15 years of age; the occasional finding of mucinous cystic tumors, usually benign, in the teenage years, and their greater frequency than other surface epithelial neoplasms; a gradual increase in frequency of all types of surface epithelial neoplasia, but particularly mucinous tumors and serous tumors as patients move through the 20s; and the rarity of metastatic neoplasia in the first three decades in general, but with occasional dramatic examples such as some Krukenberg tumors being seen in these years, as may some of the distinctive tumors of the young such as neuroblastoma. Consideration of the gross and microscopic features, and differential diagnosis, of individual neoplasms follows the introductory remarks and emphasizes the importance of gross pathology. An example of the latter is the marked difference in most cases between a dermoid cyst and an immature teratoma, the former being dominantly cystic and the latter dominantly solid, and the latter on average twice as large as the former. Caution should be exercised in entertaining a diagnosis of immature teratoma if a lesion is grossly a typical dermoid cyst. The treacherous shared gross characteristics and age distribution of the dysgerminoma and small cell carcinoma of hypercalcemic type are noted. The rarity of monodermal teratomas and malignant neoplasms such as squamous cell carcinoma arising in dermoid cysts in the first three decades is noted. The distinctive features of two recently described stromal neoplasms, microcystic stromal tumor and luteinized thecomas of the type associated with sclerosing peritonitis, are emphasized as is the varied differential diagnosis of the juvenile granulosa cell tumor and Sertoli-Leydig cell tumor. Sections on ovarian tumors and tumor-like lesions in pregnant patients and tumor-like lesions overall conclude the article.

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Introduction

The relative frequency of ovarian masses seen in young females differs from that seen in older women and there are even differences within each of the first three decades. Furthermore, in the young, many of the morphologically fascinating tumors of the ovary are disproportionately common. A cutoff of 30 years is used here because, although there are obviously exceptions, when someone is over 30 years old they are progressively at greater risk for many of the common benign and malignant ovarian neoplasms and are conversely at less risk for certain neoplasms, such as the juvenile granulosa cell tumor and the primitive germ cell tumors.

I begin by considering in broad terms the frequency of the various categories of ovarian tumors (and selected tumors within each category) during each of the first three decades and when indicated within parts of decades. These comments are aimed at highlighting one important aspect of ovarian tumor pathology, namely, that although the diagnosis ultimately rests with the light microscopic findings, it strengthens the approach to the differential diagnosis to be aware of the statistical likelihood of any diagnosis. After the introductory remarks, germ cell tumors are considered first, as primitive neoplasms in that category account for many of the malignant tumors in young women, and then the sex cord-stromal tumors, which rival germ cell tumors in their morphologic diversity, are discussed. Other well-known categories are then reviewed, emphasizing their frequency and unusual features, if any, in the young. In the second half of the period under consideration, the patient may be pregnant, and that state can be associated with a number of specific lesions and other interesting features. These are discussed in their own section. Finally, some ovarian masses are not neoplastic, and consideration of the so-called “tumor-like” lesions seen in the young concludes the article.

Two comprehensive reviews of ovarian tumors in childhood and adolescence were undertaken by Dr. Ernest Lack and colleagues in the 1980s and 1990s. In the first of these, Dr. Lack and Dr. Donald P. Goldstein presented an original report of all ovarian tumors (both neoplastic–166 cases and non-neoplastic–76 cases) seen at Boston Children’s Hospital from 1928 to 1982. Those findings were accompanied by a comment based on them as well as the established information from the literature; the latter reviewed in great detail. Treatment was also considered. Some years later, I had the privilege of working with Dr. Lack on a review article on this topic, which on this occasion was guided by Dr. Scully, who had interests throughout the entire spectrum of gynecologic pathology, but certainly, ovarian tumors in the young fascinated him, and his experience with them was second to none. My work on that review, although minor compared to that of my coauthors, and on several articles on that topic with Dr. Scully, prompted a special interest in this topic that remains to this day. The comprehensive literature review by Drs. Lack and Goldstein serves as the basis for the provision of selected references here, on the overall topic of tumors in the young, mostly defined in those articles as under 20 years, and a few other articles have been added to the list provided here, in alphabetical order, for those who may wish to study the topic in the future. Other references are then provided specific to various entities or phenomena, but due to space constraints, referencing is not encyclopedic, and standard articles can be consulted. The illustrations in this article will be biased in number to the pure stromal and mixed sex cord-stromal tumors, as the illustrations of germ cell tumors in the testis show morphology in most instances similar to that of the companion ovarian tumors. It will also be biased a little to the unusual, most readers being familiar with typical morphology.

Remarks on the frequency of entities in the first three decades

In these years, there is a much higher percentage of germ cell and sex cord-stromal tumors because (1) some tumors in these categories simply have a peak occurrence in these years, (2) surface epithelial neoplasms are less frequent than later in life, and (3) metastatic tumors are rare. This is borne out by the Boston Children’s series (even allowing for it being confined to the first two decades); 70% of the tumors were germ cell and 13% were sex cord-stromal. One-third of the former were in the primitive category, a much greater percentage than seen beyond 30 years. Surface epithelial tumors accounted for 16% of the neoplasms. Tumor-like lesions accounted for almost one-third of ovarian masses. This exceeds the figure for later years because of the relatively high frequency of follicle cysts in the first two decades, which have within them two time periods when these lesions are common, the first noted below. In another series from a children’s hospital, no less than 44% of ovarian masses were non-neoplastic.

The first decade

The first decade has a unique aspect related to tumor-like lesions, namely, the contribution to the number provided by the occurrence of follicle cysts in the neonatal period as a response to maternal stimulation. Of 76 tumor-like lesions in the Boston Children’s series, 16 were in this category. In another series, 19 of 44 non-neoplastic cysts were seen in patients less than 2 years of age. These cysts are larger than follicle cysts seen later (except those related to pregnancy), averaging 8.3 cm in the Children’s Hospital series. Their size makes them prone to torsion, with significant symptomatology as a result. Follicle cysts are rare after the first 6 months and other tumor-like lesions are rare at any time in this decade. A corpus luteum cyst rarely occurs in neonates. Dermoid cysts are rare in the first 2 years but become progressively more common thereafter. Primitive germ cell tumors are seen but are much commoner in the next two decades; in the Boston Children’s series, only one of eight patients with dysgerminoma was in the first decade. That figure notwithstanding, the dysgerminoma is much more common in the first decade than is the companion male tumor, the seminoma. The juvenile granulosa cell tumor is more common in the first decade than in any other; adult granulosa cell tumors are also seen in the young but are
uncommon in the first decade. Sertoli–Leydig cell tumors are seen occasionally, and the retiform subtype accounts for a greater percentage than any decade except the second. The sex cord tumor with annular tubules, both Peutz–Jeghers syndrome associated and unassociated, is rarely encountered in the first decade, but is most common in the second and third decades. Stromal and steroid cell tumors are seen occasionally, but are commoner in the next two decades. The small cell carcinoma of hypercalcemic type is rare before 10 years, only three examples being known. Miscellaneous other tumors such as primary sarcomas are seen, but rarely. Surface epithelial tumors of any type are rare in the first decade. One tumor with a predilection for children, the neuroblastoma, accounts for the majority of the rare cases of ovarian metastasis in children and may be seen in the first decade.

The second decade

The second decade is noteworthy for the acceleration of the frequency of all the primitive germ cell tumors as shown by the average age of occurrence of several of them being circa 19 years. One rare monodermal teratoma, the primitive neuroectodermal tumor, is seen more often in the second than in the first decade. The juvenile granulosa cell tumor is a little less common in this decade than in the first, and adult granulosa cell tumors become slightly more common but are still rare. The Sertoli–Leydig cell tumor becomes progressively more common, with the retiform variant peaking at about 15 years of age. The small cell carcinoma of hypercalcemic type begins to be seen with an accelerated pace in this decade and is only somewhat less common than in the third decade when it peaks. Surface epithelial tumors remain uncommon, although more frequent than in the first decade. Virtually the only cell types seen are serous and mucinous. In the Boston Children’s series serous slightly outnumbered mucinous. In our consultation material, mucinous tumors are much more numerous. Steroid cell tumors are seen in this decade with about 7% occurring in prepubertal girls. Pure stromal tumors, except the sclerosing stromal tumor, remain rare. Metastatic carcinomas of “adult” types that are virtually unheard of in the first decade are seen occasionally in the teenage years with well-documented examples of Krukenberg tumor, in particular. Lymphoma and leukemia involving the ovary are occasionally seen in the second decade and even before having no great predilection for any of the first three decades. Ovarian involvement by the intra-abdominal desmoplastic small round cell tumor with divergent differentiation is commonest in the teenage years. The second peak of occurrence of follicle cysts (the first being in the neonate) is seen in the second decade around the time of the menarche. From then on, the various physiologic cysts of the ovary may be seen and so also with progressing frequency as the years go by are endometriotic cysts. Two rare tumor-like lesions, massive edema and fibromatosis, may be seen in the second decade. Once patients enter the reproductive years, the various tumor-like lesions of pregnancy may be encountered.

The third decade

Germ cell tumors of all types, including the commonest of them, the mature cystic teratoma (dermoid cyst), are seen with slightly greater frequency in this decade than in the second. Secondary malignant change in teratomas and the commonest monodermal teratomas, struma ovarii and carcinoids, remain uncommon until patients pass beyond 30 years. One can rarely see this phenomenon in patients younger than 30 years, but almost never before 20 years. The third decade sees a peak in the frequency of Sertoli–Leydig cell tumors, which occur at an average age of 25 years. Of all Sertoli–Leydig cell tumors, 75% occur in the first three decades. Granulosa cell tumors of both adult and juvenile types are seen with some frequency, the adult form becoming more common than previously. Steroid cell tumors become more common as do stromal tumors, particularly the sclerosing and microcystic variants and the unusual lesions associated with sclerosing peritonitis. One significant aspect of the third decade, particularly when compared to the prior two, is the appreciably greater frequency of surface epithelial tumors, particularly as the decade moves along. For example, serous borderline tumors, which are rare before 20 years, are seen with some frequency in the third decade, although the pace of occurrence accelerates even more after the age of 30 years. Of all tumors with any malignant potential in the surface epithelial category, serous borderline tumors and mucinous borderline tumors account for the majority in the third decade. Mucinous carcinomas are occasionally seen, but less frequently than borderline tumors, and serous carcinomas remain rare in the third decade. The rare primary angiosarcoma of the ovary appears to be commoner in the third decade than in any other. Metastatic tumors of conventional adult forms become gradually more common.

Germ cell tumors

As has already been noted, these tumors account for the majority of ovarian neoplasms in the young, about 70% if one considers only the first two decades, and probably about 60% if one considers the first three decades because of the increasing frequency of other tumors, particularly surface epithelial, as the third decade goes along. The relative high frequency of these tumors in the young is in part contributed to by the rarity of certain other neoplasms, but also by the fact that primitive germ cell tumors peak in the late teens and early 20s, and in the first three decades there is a major contribution to case numbers by the frequent mature cystic teratoma, a neoplasm which may be seen at any age and is indeed the commonest of all tumors in the years of interest to us here. Mulligan25 tabulated the numbers in four series considering the frequency of primary ovarian neoplasms in the first two decades and found that dermoids accounted for half the cases.3,8,12,14 However, although dermoids have their own interesting aspects as discussed later, the germ cell tumors that have a very special predilection for the young, the primitive tumors, begin this section. In children, ovarian germ cell tumors are less common than extragonadal
examples due to a significant contribution to the numbers of the latter by sacrococcygeal neoplasms. In a tabulation of the literature, Dehner found that in children, the ovary was the second commonest site of a germ cell tumor (behind sacrococcygeum by a margin approaching 2:1), and testis was third, with the ovary exceeding the testis by about 2.5:1.

Patients usually present with the typical symptoms of a large adnexal mass. Endocrine manifestations, including virilization due to stromal luteinization, are rarely seen, and the serum HCG is typically elevated to some degree in cases in which the tumor has syncytiotrophoblast giant cells. Dysgerminoma, and exceptionally another form of germ cell tumor, may arise out of the background of a gonadoblastoma, the latter a fascinating entity reviewed in detail in a companion article.

Dysgerminoma

This is the most common tumor in the primitive group, if all ages are considered, accounting for about 50% of them. In children, the literature overall indicates that there is a more even distribution with immature teratoma and yolk sac tumor. Indeed, in the Boston Children's series of patients up to 21 years, there were about twice as many cases each of yolk sac tumor and immature teratoma. Paraneoplastic hypercalcemia has been reported rarely. Dysgerminoma is the primitive neoplasm with the most uniform sectioned surface, typically being lobulated and creamy white to tan (Fig. 1), a feature often shared with small cell carcinoma of hypercalcemic type and malignant lymphoma. The latter is the one of these three most often bilateral (circa half the time), dysgerminoma being so grossly 10% of the time, and small cell carcinoma almost never. Hemorrhage may be conspicuous in some dysgerminomas. Their average size is about 15 cm. Dysgerminoma is usually pure, but has an occasional association with gonadoblastoma and may be part of a mixed neoplasm when it is associated most often with yolk sac tumor but occasionally with other tumor types (see section on Mixed germ cell tumors).

On microscopic examination, there is most often a more or less diffuse growth, but it is interrupted to variable extents by the typical septa that characterize germinoma at all sites and with a lymphocyte-rich inflammatory infiltrate typically centered for the most part on the septa but spreading out into the cellular areas to some degree and sometimes forming lymphoid follicles; plasma cells are uncommon. Infrequent to rare findings are formations that are somewhat Sertoli tubule like and spaces that range from small and gland-like (as seen in some seminomas) to cystically dilated and occasionally follicle-like (Fig. 3). The stromal component of the tumor results in various patterns ranging from large aggregates to, more typically, small nests and a rather uniform alveolar pattern to cords (Figs. 4, 5). Caseation-like necrosis and/or hemorrhage may be seen. Punctate foci of hemorrhage may reflect aggregates of syncytiotrophoblast giant cells on microscopic examination. The latter are seen in about 3% of these tumors and are likely the cause of stromal luteinization, which is frequent in such cases.

The neoplastic cells are large and rounded with discrete cell membranes, clear to occasionally eosinophilic cytoplasm, and a central, large, rounded or angulated nucleus with coarse chromatin and one or more prominent nucleoli (Fig. 4). Mitotic figures are usually relatively numerous. The tumor cells are prone to vary in appearance due to poor fixation. There may be separation of cells obscuring the usual typical architecture, lack of visible cell membranes, eosinophilic cytoplasm, and, rarely, signet ring-like cells. The stroma ranges from delicate collagen to prominent fibrous bands, and there may be edema or, rarely, myxoid change. A granulomatous stromal reaction, usually ill defined but rarely sarcomatoid-like, occurs in 20% of tumors; Langhans'-type giant cells may be present. Most dysgerminomas stain for OCT4 (nuclear staining), D2-40 (podoplanin), SALL4, CD117 (c-kit) (membranous staining), and LIN28, but are CD30-. Occasional tumors are CK+.}

**Differential diagnosis**

Small cell carcinoma of hypercalcemic type is an important entity to be aware of, as the similar age range and gross appearance of the two tumors, the occasional association of hypercalcemia with dysgerminoma, and the presence of follicle-like space and small shrunken cells in some dysgerminomas may result in diagnostic problems. The diagnosis of
dysgerminoma in these cases rests on the presence of foci with characteristic patterns and cytology and, if needed, immunohistochemical features. Follicle-like spaces are much more common in small cell carcinoma, and a content of large cells with eosinophilic cytoplasm (often with a rhabdoid appearance) is rarely mimicked by the eosinophilic cells of dysgerminoma. Occasionally, dysgerminoma is confused with undifferentiated carcinoma, not otherwise specified, a tumor usually seen in older patients. That clinical difference is important, as if the diagnosis of undifferentiated carcinoma (non-small cell carcinoma type) is considered in the dysgerminoma age group, a suboptimally preserved dysgerminoma should be considered and appropriate immunohistochemical staining should be performed. That staining may also help when a poorly preserved dysgerminoma causes malignant lymphoma to be in the differential diagnosis. The only surface epithelial carcinoma dysgerminoma might be confused with is clear cell carcinoma. Some of the latter have a solid pattern or septa with inflammatory cells, resulting in a dysgerminoma-like nested/alveolar pattern. The shared clarity of cell cytoplasm of dysgerminoma and clear cell carcinoma can enhance the low-power resemblance between these two tumors, but well-sampled clear cell carcinomas will usually show patterns inconsistent with dysgerminoma. A clue to the diagnosis can be the finding of many plasma cells in the septa of clear cell carcinoma as they are infrequent in dysgerminoma. Should it be warranted, immunohistochemical stains will assist in this differential.

The solid pattern of yolk sac tumor may also rarely be in the differential. Its cells can tinctorially be indistinguishable from those of dysgerminoma but are generally smaller with nuclei that are not squared off and typically have less prominent nucleoli. Other helpful features include minor foci of more typical patterns of yolk sac tumors, a usual absence of lymphocytes, and, if needed, immunohistochemical differences, particularly glypican-3 positivity and OCT3/4 negativity in yolk sac tumor with the opposite results in dysgerminoma.

Yolk sac tumor

As noted in the Introduction to this issue of Seminars, we are indebted to Dr. Gunnar Teilum for most of our knowledge concerning this neoplasm, one of the few to have a book devoted to it and its “parent” structure. This tumor also peaks in the late teens and early 20s and is typically a large bulky mass with a more variegated sectioned surface than dysgerminoma. It is only rarely associated with endocrine symptoms. It is sometimes associated grossly with a dermoid cyst (Fig. 6) or may be part of a mixed germ cell tumor, when it can occasionally be recognized grossly distinct from a co-existent dysgerminoma. Another association, with high-grade immature teratoma, sometimes one with embryoid bodies (see below), is usually only uncovered on microscopic examination.

Most of the typical histologic patterns of YST (as illustrated in the testis article and so only one variant is depicted here) reflect extraembryonal (predominantly yolk sac) differentiation and include reticular-microcystic, macrocystic, labyrinthine, festoon, endodermal sinus (with Schiller-Duval bodies), parietal, and polyvesicular vitelline. Rare patterns that reflect somatic differentiation are glandular and hepatoid. Stromal luteinization has been reported in up to 25% of the cases. The tumor cells usually
have a moderate amount of pale to clear cytoplasm, a hyperchromatic often irregular nucleus, and variably prominent nucleoli. The cells lining cystic spaces may be flattened and deceptively benign in appearance. Schiller-Duval bodies (an eponym Dr. Teilum did not like), which are found in only 20% of tumors, are rounded to elongated papillae with a fibrovascular core surrounded by primitive columnar cells. The papilla may sit in a space lined by cuboidal, flat, or occasionally hobnail cells. They are usually sparse, but when numerous, create the distinctive “endodermal sinus” pattern. A picture of one of these famous structures graces the cover of a fine book on germ cell tumors.56

Two patterns described by Dr. Teilum, one in detail, the other less so, are the polyvesicular vitelline57,58 and solid59 patterns. The cysts of the polyvesicular variant may result in a striking honeycomb gross appearance and an equally remarkable macrocystic low-power microscopic appearance (Fig. 7). The cysts may exhibit eccentric constrictions; are lined by columnar, cuboidal, or flattened cells; and are separated by a loose to fibroma-like to densely cellular spindle-cell stroma (Fig. 8). Although cysts usually dominate, they are often part of a spectrum from small tubules to medium size glands to the typical cysts. In our experience, this pattern is rare, provided it is carefully distinguished from the “standard” macrocystic pattern that does not have such a “crisp” association with the stroma. Evidence suggests the polyvesicular pattern may be prognostically favorable.58

The solid pattern of yolk sac tumor may be blastema-like, hepatoid, or characterized by cells with clear cytoplasm and thus dysgerminoma-like.59 The latter is the most common of the three and is not rare as minor foci within an otherwise typical yolk sac tumor; when conspicuous, it may be problematic, but even then is still usually admixed with typical yolk sac tumor such that its nature is obvious. It may raise the possibility of a mixed germ cell tumor with both yolk sac and dysgerminoma components. Immunohistochemical differences in the staining of the two will help distinguish them if warranted.

The rarer hepatoid pattern60-63 is characterized by large polygonal cells with prominent cell borders, copious eosinophilic cytoplasm, and round central nuclei with a prominent single nucleolus, growing diffusely, in clusters or nests separated by fibrous bands. That such a pattern occurs is not surprising, as Prat et al.60 found hepatoid cells in 16% of yolk sac tumors. Hyaline bodies are often numerous. Sinusoidal-like spaces, bile, and hematopoietic elements may be seen. The immunoprofile is similar to that of hepatocellular carcinoma, including reactivity for CEA (in a canalicular pattern) and AFP. In pure or almost pure form, the hepatoid pattern is rare, and even appreciable foci in otherwise typical yolk sac tumors are uncommon. The final and least common of solid patterns has small cells with scant cytoplasm and was deemed “blastema-like” by Dr. Teilum.

Glandular differentiation in yolk sac tumor has various appearances. It is not rare to see sporadic isolated glands, or occasionally small aggregates of them; they usually appear nonspecific and are on the background of typical neoplasia, and no diagnostic issues generally arise unless glands are...
In contrast to clear cell carcinoma, YSTs are CK7-villoglandular and secretory variants. An abundant pattern resembles endometrioid carcinoma, including its associated endometriosis or adenocarcinoma. Features favoring to varying degrees clear cell carcinoma and yolk sac tumor were initially of loose, sometimes myxoid, to collagenous stroma, stellate or spindle cells, and thin-walled blood vessels. Even more unusual are foci of carcinoid, and in one case an association, in a 13-year-old girl, with fibrosarcoma.

Most typical YSTs and variants show cytoplasmic reactivity for AFP, although the staining is often focal and weak. Exceptions include the solid pattern of YST, 38% being negative for AFP in one series and the parietal and mesenchymal-like patterns are typically AFP-. Glypican-3 is a newer, more sensitive marker than AFP, typically with more diffuse and intense staining than AFP. YSTs also immunoreact for SALL4 but are negative for OCT4 (unlike dysgerminoma) as well as CD30 (unlike embryonal carcinoma). The solid pattern of YST was CD117+ in 59% of cases in one study. In contrast to clear cell carcinoma, YSTs are CK7– and EMA– or contain only rare positive cells. Focal staining for Leu-M1 can be seen in YSTs and clear cell carcinoma, but diffuse positivity favors the latter.

Differential diagnosis
As clear cell carcinoma and yolk sac tumor were initially considered one and the same, it is no surprise their distinction can still be a problem despite all we have learned over the last decades. Features favoring to varying degrees clear cell carcinoma include older age; normal serum AFP; associated endometriosis or adenofibroma; classic tubulocystic morphology; conspicuous clear cells or hobnail cells; papillae with hyalinized or hollow cores; negativity for AFP, glypican-3, SALL4, and LIN28; and positivity for Leu-M1, cytokeratin 7, EMA, and HNF-1b. Some Sertoli–Leydig cell tumors contain microcysts somewhat suggestive of reticular-microcystic yolk sac tumor, but associated patterns should aid in this distinction. Cystic follicles in some juvenile granulosa cell tumors may be somewhat evenly arrayed and separated by a thecomatous stroma, imparting a low-power picture reminiscent of the polyvesicular vitelline pattern of yolk sac tumor. However, thorough sampling will generally enable distinction because of associated patterns more typical of one or the other neoplasm and immunohistochemistry will help if warranted. Features indicative of endometrioid-like yolk sac tumor (rather than endometrioid carcinoma) include a young age, elevated serum AFP, associated typical yolk sac patterns, no squamous metaplasia, primitive-appearance nuclei, and other patterns of YST. An AFP+/CK7–/EMA– immunoprofile indicates endometrioid-like YST, and the opposite, endometrioid carcinoma. The rare yolk sac tumors of somatic derivation that have most often arisen out of endometrioid carcinoma occur in older patients, although the potential for one to occur under 30 years presumably exists.

Embryonal carcinoma
This is a rare germ cell tumor of the ovary, particularly when compared to its relative frequency in the testis. There is only one sizeable series of ovarian embryonal carcinomas; all 15 patients were under 30 years of age. For practical purposes there was an even split between the first, second, and third decades, the youngest patient being 4 years and the oldest 28 years of age. Attesting to the rarity of embryonal carcinoma is that even four of the tumors in that series were not pure, although they were predominantly embryonal carcinoma. Abnormal hormonal manifestations, likely due to high hCG levels, were common and included precocious puberty and hirsutism. Grossly, the tumors are typically large and malignant-appearing, and microscopic features are identical to those of the familiar testicular neoplasm and so are not reviewed here.

Differential diagnosis
The differential diagnosis with other germ cell tumors is essentially as considered in the article on the testis. It should be noted that for each gonad the old literature often refers to cases that would now be recognized as yolk sac tumor as embryonal carcinoma, sometimes proceeded by the word infantile, when they occur in the young, which makes literature review difficult. The differential diagnosis in the ovary between embryonal carcinoma and juvenile granulosa cell tumor is somewhat more realistic than in the testis, although even in the ovary it should rarely be a problem. The greater pleomorphism of some juvenile granulosa cell tumors in the ovary, compared to the testis, and the greater number of tumors encountered in the ovary simply may make this come up more frequently. However, the follicles of the granulosa cell tumor should be distinguished readily from the glands of embryonal carcinoma, and the atypia in the juvenile granulosa cell tumor is more spotty and variable than the diffuse pleomorphic primitive-appearing nuclei of embryonal carcinoma. Immunohistochemistry will aid if warranted. We have seen one very poorly differentiated Sertoli–Leydig cell tumor, which, in areas, was indistinguishable from embryonal carcinoma, but other foci aided the differential diagnosis.

Choriocarcinoma
This rare neoplasm may be of gestational or nongestational origin, the former occurring after puberty and having a better prognosis and the latter both before and after puberty. Pure choriocarcinoma of germ cell type is rare, it being more common to find choriocarcinoma as a component of a mixed germ cell tumor. In a report of six ovarian choriocarcinomas, four patients were in the first three decades, the youngest being six, but that two were in the fourth decade indicates the tumor may be seen at any time in the reproductive era. Prepubertal patients may present with precocious puberty and all patients are prone to present with metastatic disease. Grossly, the neoplasms are typically bulky and hemorrhagic, and microscopic examination shows the well-known features. Molecular studies may aid in determining if a neoplasm is gestational or nongestational.
Immature teratoma

These tumors are considered before the more common dermoid cyst because immature teratoma falls in the primitive germ cell group and, like all such tumors, tends to occur in the first three decades, although they may be seen at any time in the premenopausal era. Immature teratomas may be seen in both gonads and at diverse extragonadal sites including the sacrococcygeum. The ovary was the commonest location, accounting for 37 of 60 cases, in a large series of pediatric cases. In that series, there were seven in children up to 3 years old, eight from then to 10 years, and eight in children older than 10 years. However, in another series there were 20 sacrococcygeal cases and 16 ovarian. Immature teratomas usually present with nonspecific mass-related symptoms, but occasionally, the history is noteworthy because an ipsilateral dermoid cyst has been resected previously. The risk of an immature teratoma in such patients may be increased if the dermoid cysts are bilateral, multiple, or associated with rupture. Endocrine manifestations are rare, and if present, suggest the possibility of a minor unsampled component of another tumor type. The patients are typically in the early years of the reproductive era with an average of about 19 years.

The median diameter of immature teratomas is on the order of 16–20 cm, and although there are, as expected, some slight variations series to series, they all speak to a usually large size. In one report, 19 of 32 tumors were 15 cm or larger, with the smallest being 9 cm. In another series, only 6 of 54 with known size were less than 10 cm (smallest 7 cm), and 24 each were in the 10–19.9 cm and 20 cm and over groups; capsular rupture is quite common. Finally, in another report, their average size was 17.9 cm compared to 8.7 cm for mature cystic teratomas. In that pediatric experience, there were 15 cases compared to 78 mature cystic teratomas. The tumors are almost invariably unilateral, in contrast to mature teratomas, which are bilateral in a small minority (see below).

Immature teratomas typically have a predominantly solid cut surface that is fleshy, gray to pink, often with focal hemorrhage and necrosis (Fig. 9). Cysts may be seen punctuating the dominant gross appearance of most tumors, and in one study, 1/3 of the tumors had “relatively large cystic areas.” In another series, 9 of 20 tumors had a “predominantly multilocular cystic pattern.” Although dermoid cyst components are grossly evident in 25% of tumors, the overall gross features are in most cases in marked contrast to that of dermoid cysts. Not surprisingly, the larger tumors have a tendency to be at a higher stage than smaller ones.

Microscopic examination shows the well-known varied elements of any teratoma, but is dominated particularly in higher grade tumors by conspicuous foci of immature neuroectodermal tubules (Fig. 10) and cellular mitotically active glia. The diagnosis of immature teratoma almost invariably rests on finding these elements, particularly the first, albeit the other tissues present, such as mesenchymal, often appear immature also. As considered in the polyembryoma section, that neoplasm can conceptually be considered the most primitive of all immature teratomas and accordingly, some immature teratomas, particularly when high grade, contain embryoid bodies and these may show varying degrees of proliferation to yolk sac tumor, often of small amount, then technically placing the tumor in the mixed malignant germ cell tumor category (Fig. 11). The association between high-grade teratoma and finding yolk sac tumor elements, more than with lower grade immature teratomas, indicates that all immature teratomas should be rigorously sampled, particularly if high-grade and embryoid bodies are present, to exclude foci of yolk sac neoplasia, which may be overlooked. Truly minute foci of yolk sac tumor may not impact prognosis, but more than minimal foci of yolk sac tumor are likely to be of prognostic relevance. Some of the rare immature teratomas reported to have an elevation of the serum AFP level have had “yolk sac vesicles” potentially explaining the serum finding, but rarely intestinal-type glands in immature teratomas have stained for AFP. In one report, 5 of 32 immature teratomas had an elevation of the AFP level and all were reevaluated to exclude foci of yolk sac tumor and none was found. An uncommon finding in some immature teratomas is a striking proliferation of mostly small, thin-walled, closely packed vessels that form trabeculae or small nests, a finding that may incorrectly suggest immature elements or a vascular neoplasm. This is discussed in more detail emotionally.
detail in the section on dermoid cysts. Rare immature teratomas are predominantly composed of primitive endodermal elements. One unusual immature teratoma in a 17-year-old girl had a predominant component of malignant retinal anlage tumor.

Over the years, immature teratomas generally have been divided into three categories using a well-known semi-quantitative scheme, but it is hard to apply in practice, and most now use a low-grade and high-grade binary split in which grade 2 and grade 3 are grouped together. In general, the distinction between low grade and high grade is not difficult, but there will be occasional cases in which placement is a challenge because of the varied mixture of mature and immature elements in individual areas of different tumors and, for that matter, even on individual slides.

Implants, or nodal metastases, of immature teratomas are usually immature but rarely consist exclusively or mainly of mature glial tissue (“peritoneal gliomatosis”), usually in the form of small rounded foci, typically about 3 mm or so, that can be numerous. In the original series by Robboy and Scully, 10 of the patients were under 20 years, with the youngest 16 months old. Generous sampling of the implants is important as immature implants may coexist with mature implants. Mature epithelial elements, mature cartilage, endometriotic tissue, or endosalpingiosis are occasionally admixed with the glial implants. Rarely, mature glial implants are associated with a florid vascular proliferation of the type noted above. They may also be associated with endosalpingiosis or endometriosis. One article has specifically looked at glial implants in children and adolescents. Eight of the 13 patients had grade 1 immature teratomas, four had grade 2, and one had grade 3 neoplasms. The patients were aged 2.9–18.6 years (median = 11.5 years).

**Differential diagnosis (including brief consideration of sarcoma arising in primitive germ cell tumors)**

The differential diagnosis of an immature teratoma includes a mature teratoma of so-called solid type. The latter does not have the gross features of a dermoid cyst but rather those of an immature teratoma, but it lacks the embryonal tissues required to diagnose the latter. Also in the differential diagnosis is the much more common mature cystic teratoma (dermoid cyst). These tumors are usually smaller, and, as their name implies, dominantly cystic. The latter is in marked contrast to the much more heterogeneous solid and cystic sectioned surface, often with hemorrhage and necrosis within the solid component, of an immature teratoma. It is important practically to be aware of these gross differences, because otherwise, typical dermoid cysts may on microscopic examination have a number of incidentally discovered findings that may cause concern for immaturity, but the bias should be away from that diagnosis if the gross characteristics are typical of a dermoid. Even minor foci of immaturity in a dermoid cyst are allowed as discussed elsewhere. The diagnosis of immature teratoma requires embryonic-appearing tissue, and not just fetal-type tissue, and the presence of fetal cartilage or other fetal-appearing tissues in a dermoid cyst often leads to a misdiagnosis of immature teratoma. Dr. Scully once commented that it might have been better if the designation of immature teratoma had been replaced by embryonal teratoma (a term used occasionally, particularly in the older literature) to emphasize the requirement of embryonal-appearing, as opposed to simply fetal-type, elements.

The diversity of elements in immature teratomas, and their nature, generally readily enables distinction of this tumor from various other neoplasms that have shared elements such as cartilage and skeletal muscle. In the age group in which immature teratomas are likely to be encountered, a consideration may be Sertoli–Leydig cell tumor with heterologous elements, because the mucinous epithelium of such neoplasms, particularly if associated with cartilage and skeletal muscle, may suggest teratoma. The presence of typical Sertoli and Leydig elements in their various guises should enable the diagnosis of a Sertoli–Leydig cell tumor to be made, and the latter do not contain squamous epithelium, sebaceous glands, and (if one excludes one rare case) glia as seen in teratomas. The ovarian tumor that has cartilage and skeletal muscle most often is the malignant mixed mesodermal tumor (carcinosarcoma), but it occurs at an older age and almost invariably has easily recognizable surface epithelial carcinoma components. It also only exceptionally has a neuroectodermal component. Another tumor that may enter the differential diagnosis is the mesodermal adenosarcoma, because sometimes the more orderly growth of that neoplasm and lack of the obviously malignant surface epithelial components of the usual malignant mixed mesodermal tumor may make the resemblance to an immature teratoma somewhat greater, at least in areas. The typical frond-like architecture and cuffing of stroma around glands should enable adenosarcoma, even with heterologous stromal elements, to be distinguished from immature teratoma, and its components are less heterogeneous than those of a teratoma. Although the ovarian adenosarcoma occurs in a somewhat younger age group, on average, than carcinosarcoma, it is rare in the first three decades.

A difficult issue in the interpretation of occasional immature teratomas is distinguishing a pure teratoma from a sarcoma, usually a rhabdomyosarcoma, arising within one. To diagnose the latter, one needs to see “overgrowth”
of the immature skeletal muscle components of a teratoma. This is not always an easy judgment because some high-grade immature teratomas may have scattered somewhat impressive foci of immature skeletal muscle. The point at which this has “overgrown” the underlying tumor is imprecise in some cases. Obviously, confluent massive destructive overgrowth of skeletal muscle will make a diagnosis of rhabdomyosarcoma arising out of immature teratoma straightforward, but more subtle cases can be problematic. If doubt remains, a cautionary note is appropriate.

Although tumors arising in teratomas (excluding mucusin cystic tumors) are usually the monodermal teratomas and somatic carcinomas, such as squamous cell carcinoma, that arise in dermoid cysts, as just alluded to occasional sarcomas arise on the background of immature teratomas and mixed germ cell tumors, particularly those with an immature teratoma component, because the mesenchyme of that element that can produce a sarcoma. In a report of 46 examples occurring in germ cell tumors of diverse sites (the majority were in the mediastinum), there were three ovarian examples, all from patients in the third decade.84 One tumor was immature teratoma with embryonal rhabdomyosarcoma; the second mature teratoma, embryonal carcinoma, and leiomyosarcoma; and the third dysgerminoma, immature teratoma, and embryonal rhabdomyosarcoma. All patients were alive after chemotherapy, but follow-up exceeded 2 years in only one of them.

Polyembryoma

This neoplasm is considered at this juncture because, although it contains yolk sac and embryonal carcinoma epithelium and accordingly some consider it a particular form of mixed germ cell tumor, Dr. Scully, because of the almost invariable presence of teratomatous elements and because by his concept immature teratoma, definitionally, must have embryonal elements, considered the polyembryoma an exceedingly immature teratoma in as much as its constituent part, the embryoid body, recapitulates embryonic development at an early stage of gestation, circa 12 days. This approach is taken in the recent World Health Organization (WHO) Classification. It is debatable whether an ovarian tumor composed entirely of embryoid bodies, and therefore a “pure polyembryoma,” has ever been encountered, and all those reported have had some other germ cell component. However, the diagnosis of polyembryoma is tenable when there is a dominant population of embryoid bodies with, additionally, teratomatous elements. Although the WHO does not accept polyembryoma as a separate entity, we do so here to better highlight this fascinating pattern of germ cell neoplasia.

A component of embryoid bodies, and if numerous enough, warranting the polyembryoma designation, is most often seen in a mixed germ cell tumor, often containing components of teratoma, yolk sac tumor, and embryonal carcinoma, as the latter two tumor types may arise from the yolk sac and embryonal carcinoma epithelium present as a constituent of the embryoid body. Indeed, it is not rare to see microscopic foci of yolk sac tumor or embryonal carcinoma emanating from an embryoid body, and it can be debatable sometimes as to whether the proliferation is enough to warrant a separate diagnosis of yolk sac tumor or embryonal carcinoma. An arbitrary cutoff of 3 mm is used by us to warrant separate tumor components being diagnosed.

No more than 10 polyembryomas have been reported and four have occurred in the first three decades, ages being 9 years (two cases), 17 years, and 26 years.95-98 The usually large tumors have soft, reddish-brown, spongy to microscopic, and hemorrhagic sectioned surfaces. The definitional microscopic feature is the presence of numerous small structures resembling early embryos scattered within an edematous stroma (Fig. 12). Although based on a testicular example from a 41-year-old man, the descriptions and illustrations of Evans more than 50 years ago cannot be improved upon.99 The classic well-formed embryoid body consists of two cavities (amniotic and yolk sac) separated by an embryonic germ disc (Fig. 13). The latter is composed of epithelium resembling that of embryonal carcinoma underlain by thin, flattened AFP+ epithelium of yolk sac type. As these structures are occurring in neoplasms, it is not surprising that most embryoid bodies are imperfectly formed (Fig. 14), particularly when the embryonal-type or yolk sac-type epithelium forms microscopic carcinomas. In these cases, one can still see a somewhat orderly spatial distribution of embryonal and yolk sac epithelium in a generally round-to-oval aggregate and separated by the typical edematous stroma. Syncytiotrophoblastic giant cells are usually associated with some of the embryoid bodies or are isolated in the stroma. Hepatoid cells may rarely be seen.100

Mixed germ cell tumors

Most tumors in this category are admixtures of more than one primitive tumor type (so-called mixed malignant germ cell tumors), but other mixed forms of neoplasia in the germ cell tumor category occur. Dermoids with malignant transformation are by convention considered separately, as they are later here. It is often not emphasized that there are occasional mixed germ cell tumors that are malignant, but

Fig. 12 – Polyembryoma. The typical low-power appearance of numerous embryoid bodies sitting in a somewhat orderly arrangement within a background of loose stroma is seen.
The mixture is not of two or more primitive tumors in the same mass, but rather the enigmatic occasionally encountered circumstance in which a dermoid cyst is in direct continuity with a primitive germ cell tumor. The commonest association is that of some dermoids with an immature teratoma, but occasionally and remarkably, there may be juxtaposition of a dermoid cyst with yolk sac tumor or choriocarcinoma. The admixture of an entirely benign germ cell tumor and a highly malignant one as part of the same neoplastic process within the ovary is one of the most remarkable examples of the strange combinations one may see in neoplasia. Based on our own experience and that in the literature, the least common admixture is dermoid cyst with dysgerminoma.

The mixed primitive tumors are less common than in the testis, where their counterparts account for roughly one out of three testicular neoplasms. In the ovary, the figures have varied in different studies but only about 8% of malignant germ cell tumors are of this type. In the series of Kurman and Norris,101 eight patients were in the first decade, 12 in the second, and 10 in the third. Any admixture can be seen, a common one being yolk sac tumor with dysgerminoma, which accounted for 11 of 30 mixed tumors in one series.101 One of those we honor in these pages, Dr. Santesson, was the senior author of one of the earliest investigations of mixed germ cell tumors, and he was one of the first to point out the frequency of yolk sac elements within them.102 In accord with the concept that polyembryoma is the most immature of all teratomas, and as its unit the embryoid body often gives rise to scattered foci of yolk sac tumor, it is not surprising that another common admixture is immature teratoma and yolk sac tumor. In a series looking at all tumors with an immature teratoma component, 37 of 86 were pure immature teratoma and the remaining 49 additionally had yolk sac tumor accompanied in a minority by other primitive components.77 In another report,37 11 of 17 tumors with only two components were immature teratoma and yolk sac tumor. Essentially, any random arrangement of the various forms of primitive germ cell neoplasia may be admixed in any combination. In our experience, foci of choriocarcinoma are infrequent, although it is common to find syncytiotrophoblast giant cells, whose presence sometimes leads to an “over-diagnosis” of choriocarcinoma, the latter diagnosis requiring the additional presence of cytotrophoblast. Undoubted foci of choriocarcinoma may be seen, being present in 16% of the cases in one series.37

**Solid mature teratoma**

Brief mention only is warranted for this rare neoplasm. As best we can tell, Peterson was the first to emphasize the gross similarity to the more common immature teratoma (and gross difference from the mature cystic teratoma), but also stress the lack of embryonal features such that the diagnosis of immature teratoma was not warranted. Three of the four cases reported by him were girls of 10, 13, and 15 years.91 Prior to his report, and even to a degree after it, the “solid teratoma” diagnosis had sometimes been used for cases that were clearly mixed malignant germ cell tumors. Two of the four solid mature teratomas later reported by Thurlbeck and Scully37 occurred in teenagers. There is perhaps not an area of ovarian tumor evaluation where thorough sampling is more crucial than this one so that minor embryonal (immature) elements, or even potentially more significantly non-teratoma elements, are not missed. As an example of that, a mid-1970s article of cases that grossly were considered “solid teratoma” had yolk sac elements in six of them and all were rapidly fatal.79

**Dermoid cyst (mature cystic teratoma)**

This is the germ cell tumor with the widest age distribution; most are seen in the reproductive years, but they may be seen in children and the elderly.103-107 In one large series, about
90% of the tumors were seen in patients between 15 and 50 years of age, with a majority being in the third decade.\textsuperscript{106} They are rare in the first 5 years of life, but one is documented in a 5-month-old, and in one series, almost 2% occurred in patients under 14 years of age.\textsuperscript{104} In the Mayo Clinic series, 1% were from patients in the first decade, and 3% of the patients were in the second decade.\textsuperscript{105} The symptoms are usually nonspecific, but a variety of unusual manifestations may result in cases of great clinical interest. They were reviewed in detail by Pantoja et al.\textsuperscript{108} and also remarked upon by Dr. Scully in his fascicle, so are not repeated here, with the exception of mention of a striking entity of neurologic type recognized since that time, and the subject of considerable recent interest. In these cases, patients with dermoids have autoimmune encephalitis due to antibodies against the N-methyl-D-aspartate receptor.\textsuperscript{109} This appears to be more common than other autoimmune disorders, such as hemolytic anemia, long known to complicate some dermoids.

The literature indicates a frequency of bilaterality on the order of 10–12%. This may be synchronous or metachronous.\textsuperscript{110} Dermoid cysts are smaller on average than immature teratomas. In a comprehensive study, 60% of the tumors were between 5 and 10 cm, 12% less than 5 cm, 20% between 10 and 15 cm, and the small remainder greater than 15 cm.\textsuperscript{104} The average size in the literature overall is generally in the 6–8 cm range. Sectioning shows them to be typically unilocular (about 90%) cysts, but occasionally two or more cysts are seen. Their typical components of hair, teeth (about 25% of cases), and Rokitansky’s protuberance need no elaboration; they rarely may have conspicuous brain-like tissue.

The often interesting but at the same time easily recognizable appearance of most dermoids (Fig. 15) is important because, as noted earlier, most lesions that are typical dermoids grossly do not turn out to be anything else after microscopic evaluation. Of course, careful gross inspection is needed to exclude, for example, squamous cell carcinoma arising within one. Occasionally, there are findings in grossly typical cases that may cause concern; this often is cerebellum, but may also include diverse other findings such as ependymal tubules and pituitary tissue. Although of academic interest, these do not represent “immature” elements, which, as noted above, should be of embryonic type. Similarly, the microscopic foci of fetal-type tissues encountered in many otherwise typical dermoid cysts also have no clinical significance and should not lead to the diagnosis of immature teratoma. Even tiny foci of embryonal tissue are allowed in some otherwise typical dermoid cysts. The miscellaneous unusual findings in dermoids can be seen in tumors of the young, one example being prostate tissue that occurred in patients with a mean age of only 31 years in our report of four cases, the youngest being a 17-year-old.\textsuperscript{111} One rare variant of dermoid cyst is the fetiform teratoma (so-called homunculus); two-thirds of the reported cases of this rare lesion have been in patients up to and including 30 years of age.\textsuperscript{112}

The neuroectodermal elements can incite a florid vascular proliferation. In the only series of cases of this phenomenon occurring in the ovary, three of the five tumors were mature cystic teratomas, although one did contain a microscopic focus of primitive neuroepithelium.\textsuperscript{86} The fourth tumor was an immature teratoma and the fifth an immature teratoma with a minor component of yolk sac tumor. Although this finding may have some consequence in an immature teratoma, potentially suggesting an angiosarcoma, it is perhaps even more problematic when found in a mature cystic teratoma because it may then, if misinterpreted, move a benign neoplasm into a malignant category, potentially an immature teratoma, or again angiosarcoma. The particular features of the vascular proliferation, typically long, thinned-walled, curved vessels, or sometimes a solid glomeruloid arrangement, are crucial to its recognition, and, as in so many areas of pathology, simple awareness of the process will be crucial in leading to it being interpreted correctly. In one other case of this phenomenon in a 25-year-old, the vascular proliferation was associated with Wagner–Meissner-like corpuscles.\textsuperscript{113} Chen et al.\textsuperscript{114} found foci resembling ectopic meningotheial hamartomas in 40% of dermoid cysts that occurred in patients with a mean age of 36 years, the youngest 23 years. They abutted cranially derived tissues, especially scalp-like skin and glial tissue. Anastomosing slit-like channels lined by flat to cuboidalEMA+ cells were arranged within dense collagen bundles; pigmented dendritic cells and psammoma bodies were also typically present. In the cases associated with NMDAR encephalitis, marked lymphoid infiltrates around mature glial elements, sometimes with reactive germinal centers, diffuse lymphoplasmacytic infiltrates within the neuroglial matrix, and degenerative neuronal changes have been described.\textsuperscript{109} In some cases, as noted earlier, dermoids, particularly if bilateral or multiple, recur as primitive germ cell tumors, usually immature teratoma.\textsuperscript{84}

### Monodermal teratomas

#### Neuroectodermal tumors

Although these are amongst the least common of the so-called monodermal teratomas, they are considered first here because they are the group that has the greatest tendency to occur in the young. These rare tumors closely resemble neuroectodermal tumors of the central nervous system or rarely those of peripheral type.\textsuperscript{115–119} Although not all may be

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**Fig. 15 – Dermoid cyst from a child.**
of teratomatous origin, most are, and it is most convenient to consider them as a group. The largest reported series divided the tumors into three categories: differentiated, primitive, and anaplastic. Only one of the six differentiated tumors occurred in the first three decades (a 16-year-old). However, 8 of the 12 primitive tumors were seen in this age group, five being teenagers and three in their 20s. Finally, all seven anaplastic tumors occurred in the first three decades, one a child of 6 years, four teenagers, and two in their early 20s. The tumors are usually large and have no distinctive gross appearances unless a dermoid is appreciated. The differentiated tumors are ependymomas (Fig. 16), the primitive ones resemble neuroblastoma, primitive neuroectodermal tumor, medulloblastoma, and ependymoblastoma, and the anaplastic ones resemble glioblastoma multiforme. Minor foci of mature teratomatous elements are commonly present in the primitive and anaplastic tumors, but not in ependymomas with one exception to date. As with the issue of rhabdomyosarcoma arising out of immature teratoma, considered earlier, it may be difficult on occasions to determine when a small-volume primitive neuroectodermal tumor is arising out of the background of a teratoma. A similar appreciation of an unequivocal confluent overgrowth will warrant the diagnosis of a tumor arising from the teratoma as opposed to morphology consistent with the neuroectodermal elements that typify high-grade immature teratomas. A background teratoma can be crucial in suggesting the diagnosis of a neuroectodermal tumor as opposed to other considerations, which may arise in a pure neoplasm, such as the broad differential diagnosis of a so-called small round cell malignancy. The diagnosis of ependymoma, the tumor in the group with the widest morphological spectrum, is aided by its typical reactivity for GFAP. In a study of primitive neuroectodermal tumors, Euscher et al. found staining for the following markers in descending order of frequency: neurofilament, CD56, S100, GFAP, CD99, and synaptophysin. Kawauchi et al. found that a primitive tumor contained a chromosomal translocation specific for PNET/Ewing’s sarcoma and EWS/FLI-1 chimeric RNA.

**Struma ovarii**

This is the commonest of the monodermal teratomas, but it is uncommon in the first three decades. In a review of the literature, only 15% of the patients were under 30 years, the vast majority of that group being in the 20s. There were only two younger, one teenager, and a girl aged 6 years. In a later series from the Mayo Clinic, only one patient, a 19-year-old, was under 30 years. In two articles on struma ovarii from our group, the youngest in each was 23 years old. Although there are, to the best of our knowledge, no features unique to struma in the young, as this is the most common monodermal teratoma, mention of some of its interesting characteristics is warranted.

This neoplasm is typically incidentally discovered when an adnexal mass that is fundamentally a dermoid cyst is removed, but other features may draw the patient to medical attention. Rarely, hyperthyroidism may be related to struma, but a more common problematic finding is the presence in about one-third of cases of ascites, occasionally accompanied by Meigs’ syndrome. The association of a pelvic mass, ascites, and even, in some cases, an elevated serum level of CA125 can mimic cancer, and if the microscopic features are unusual (see below), a misdiagnosis of carcinoma is possible. The gross characteristics in cases of struma depend on the nature of the associated neoplasm, if any, and the prominence of the struma component. Struma may be pure, but is most commonly associated with another tumor, usually a dermoid cyst. Less commonly, a carcinoid tumor in the form of strumal carcinoid, a Brenner tumor, or a mucinous tumor is present. Struma may form a unilocular or multilocular cyst with colloid-like contents, potentially mimicking a cystadenoma. The tumor tissue typically is red and soft, but, when cellular, gross appearances that overlap with those of other tumors are not rare. A solid consistency is common in the latter cases, and the color can vary from tan to brown or even green. Either of the latter two colors should suggest struma, particularly if there is an associated dermoid.

The microscopic features of struma in most cases are straightforward, but cellular forms may cause significant diagnostic difficulty. Tumors with solid oxyphilic morphology raise the broad differential diagnosis of ovarian tumors in general with this tinctorial characteristic including steroid cell tumor and many others. The second major problematic feature is clear cells. They may bring into the differential diagnosis diverse ovarian tumors with clear cells, including clear cell carcinoma. In both these situations, the relatively uniform cytology, occasional association with a dermoid cyst (thorough sampling being crucial), lack of patterns of other lesions, and, if needed, immunohistochemical staining for thyroglobulin and TTF1 will solve the problem. The latter also help in cases of cystic struma. The cysts in such cases are often lined by indifferent flat to cuboidal epithelial cells. Isolated tiny thyroid follicles between the cysts may be a clue to the correct diagnosis.

Thyroid-type carcinomas derived from struma are rare, but a subject of recent interest. Surprisingly, 11 of 27 cases of malignant struma in a recent study were from patients under 30 years. The diagnosis of malignancy requires the presence of the histologic features of thyroid carcinoma.

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**Fig. 16 – Ependymoma. Typical perivascular pseudorosettes are seen.**
and/or evidence of malignant behavior. Almost all of the histologically malignant tumors are papillary or follicular carcinomas, which occur with approximately equal frequency. A diagnosis of follicular carcinoma requires unequivocal features of malignancy using basic principles, evidence of invasion of normal (ovarian) tissue or vessels (although vascular invasion is rare), or metastasis. A number of clinically malignant strumas are highly differentiated, histologically resembling normal thyroid tissue or more often follicular adenoma. Large size and the presence of adhesions probably heighten the risk of a malignant behavior, as they have been present in some cases that have behaved in a malignant fashion but could not have been called malignant using the standard histological criteria. Extraovarian spread, usually found at oophorectomy, is typically in the form of peritoneal implants resembling normal thyroid tissue (“peritoneal strumosis”). Rarely, malignant struma can mimic an ovarian surface epithelial carcinoma (usually endometrioid carcinoma) or potentially almost any ovarian tumor. The features of malignant struma have been presented in detail recently and are not considered further here.

**Carcinoid tumors**

This is the second most common monodermal teratoma. The largest original series of insular carcinoids reported, which included a comprehensive literature review, and totaled in aggregate 48 cases, did not have a single example in a person in the first three decades, the youngest patient being 31 years. Doubtless sporadic cases have been seen or reported (we have not exhaustively reviewed the literature), but it is clearly rare in the young. The same group of authors in their report of 18 trabecular carcinoids, did, on the other hand, perhaps surprisingly, have as many as three patients in the third decade. In the original report defining strumal carcinoid, only 2 of 50 patients were in the first three decades, again both being in the third decade.

As in older patients, these lesions vary from solid masses that have effaced the underlying parent dermoid to smaller masses easily identifiable on the background of a dermoid. In insular tumors, a predominant pattern of discrete cellular nests, sometimes punctured (particularly at their periphery) by small, round acini, are separated by a scanty to abundant fibromatous stroma. Eosinophilic secretions, which may undergo psammomatous calcification, are often found in the acini. Dilated acini may mimic true glands. A strumal carcinoid is simply an insular or trabecular carcinoid, or neoplasm with both elements, associated intimately with struma. Since strumal carcinoids are much more common than trabecular carcinoids, the latter should be diagnosed only after thorough sampling has excluded a struma component. A confusing aspect of about 40% of strumal carcinoids is the presence of glands or cysts lined by mucinous epithelium. This does not warrant the designation mucinous carcinoid. In pure trabecular carcinoid or that component of a strumal carcinoid, long parallel ribbons of columnar cells with oblong nuclei oriented perpendicular to the axis of the ribbon are seen. The tumor cells of carcinoids usually have moderate amounts of eosinophilic cytoplasm that is most appreciable in cells lining the acini and at the periphery of the nests; reddish-brown argentaffin granules are often present. Rarely the cytoplasm is particularly abundant, imparting an oxyphilic appearance. Mucinous carcinoid is the least common ovarian carcinoid. In the largest study of them, they were rare in the young, but one of six well-differentiated tumors occurred in a 21-year-old and one of eight cases with a carcinoma component occurred in a girl aged 14 years.

**Other monodermal teratomas**

These are rare but enigmatically have often occurred in the young. Examples include a pituitary adenoma responsible for Cushing’s syndrome, three neurogenic cysts, an ependymal cyst, and a cyst of respiratory type.

**Dermoid cyst with malignant transformation**

Malignant transformation of a dermoid is more common in the elderly patient, but three of 19 cases of squamous cell carcinoma arising in a dermoid reported by Pins et al. were in patients aged 21, 25, and 30 years. One other patient in that series, with a squamous cell carcinoma and associated endometriosis, was a 29-year-old, and another patient without either a dermoid or endometriosis was a 27-year-old. When we reviewed this topic in the early 1990s, we found at least one example in the first decade and seven in the second. The tumors are usually larger than typical dermoid cysts with obvious suspicious areas grossly. Squamous cell carcinoma, which is almost always invasive, accounts for 80% of the tumors. Most are typical, but some have had a prominent papillary (or verrucous), sarcomatoid, or undifferentiated component, the last sometimes being composed of oxyphilic cells. The differential diagnosis of squamous cell carcinoma arising in a dermoid may be very dependent on thorough sampling if the cancer is large. Occasional endometrioid carcinomas have massive squamous differentiation, but finding a dermoid or, alternatively, neoplastic endometrioid glands will be definitive. Malignant melanomas can rarely arise in dermoid cysts. In the largest series of cases of definite or probable primary melanoma, 2 of the 9 patients were under 30 years, one was an 18-year-old, and one was a 21-year-old. Sarcomas can also complicate dermoids rarely, two of seven angiosarcomas (almost all from patients under 30 years) in one report being of that nature.

**Sex cord-stromal tumors**

This category contains both pure stromal tumors and tumors with both stromal and sex cord components, and some of the former and many of the latter have a predilection for the young. We consider stromal tumors first.

**Sclerosing stromal tumor**

Dr. Scully became aware in the mid to late 1960s that there was a distinctive constellation of findings that set a particular stromal neoplasm apart from others in the group. One of those features was its tendency to occur in the young, with 80% seen before 30 years and the average age 27 years. He
appreciated also distinctive microscopic features and frequent different gross characteristics from the more common stromal neoplasms, the fibroma, and thecoma. As a prominent, often sclerotic, stroma is one of its several typical features, he designated it “sclerosing stromal tumor.” Most such tumors present in a banal manner with nonspecific symptoms or are an incidental finding. Rarely they have been associated with androgenic manifestations. Although stromal tumors associated with Gorlin’s syndrome are almost always fibromas, there is one reported case of virilizing bilateral sclerosing stromal tumors in a patient with this syndrome. That case also represented the potential for pregnancy to be associated with virilization due to, presumptively, the high HCG level of that condition causing the usual inert luteinized cells to be more active.

The tumor is usually unilateral, with a solid white-to-yellow cut surface, and commonly has edema and cyst formation; the last two features are sometimes striking (Fig. 17). Although some of these neoplasms, if uniformly solid, can be indistinguishable from fibromas and thecomas, in general; they have a more variegated appearance. Cystic change is much more typical of the sclerosing stromal tumor, and occasional examples are dominantly cystic, which is exceptional for other stromal neoplasms.

The histologic hallmarks are a pseudolobular pattern of cellular regions surrounded by hypocellular collagenous (Fig. 18), edematous, or, rarely, myxoid areas (Fig. 19); a jumbled admixture of spindled and rounded, vacuolated to uncommonly overtly luteinized cells (Fig. 19); and, finally, ectatic vessels, which when prominent and aggregated, may impart a hemangiopericytoma-like look (Fig. 20). The luteinized cells, which are typically vacuolated rather than having conspicuous eosinophilic cytoplasm, tend to be of the latter nature, and more conspicuous, when the patient is pregnant.

Differential diagnosis

Many fibromas are somewhat vascular, but they lack the typical pseudolobulation and admixed fibroblasts and lutein cells of the sclerosing stromal tumor. A fibroma may have lutein cells, but a jumbled arrangement with fibroblasts is not seen. It should be noted that as with any area of neoplasia, there is overlap and that is certainly so here, for example, occasional sclerosing stromal tumors have zones that in isolation would warrant the diagnosis of fibroma. Occasionally, sclerosing stromal tumors have a striking paucicellular myxoid stroma and can bring myxoma into the differential diagnosis. Finding distinctive foci of sclerosing stromal neoplasia is obviously crucial. The possible relation with myxoma that some have proposed is discussed later in the myxoma section.

As with sex cord-stromal tumors in general, the morphology of the sclerosing stromal tumor is often somewhat altered in pregnancy, making it more difficult to diagnose in that setting. As the tumor peaks at about 27 years, it is self-evident that some will be found during pregnancy. The lutein cells in these patients typically have abundant eosinophilic cytoplasm and are more striking and diffuse in their distribution than in the usual case such that the typical lobulation and even vascularity may be obscured, at least in regions. Small foci, sometimes at the periphery, will show the more distinctive morphology. The differential diagnosis with a

![Fig. 17 – Sclerosing stromal tumor. This neoplasm shows particularly conspicuous edema with cystic degeneration.](image1)

![Fig. 18 – Sclerosing stromal tumor. The typical pseudolobular pattern with prominent stromal edema is seen.](image2)

![Fig. 19 – Sclerosing stromal tumor. Lutein cells are somewhat more striking than is sometimes the case, likely due to the patient being pregnant. The stroma of this neoplasm is occasionally myxoid, as illustrated here.](image3)
steroid cell tumor may arise. This and other issues in pregnancy are considered in detail elsewhere.\textsuperscript{142}

Luteinized thecoma of the type associated with sclerosing peritonitis

Some years after Dr. Scully defined the sclerosing stromal tumor as an entity, he began to see occasional remarkable examples of ovarian masses that appeared to represent strange tumors in the stromal category but which were associated with sclerosing peritonitis. Because he felt these were neoplasms of stromal derivation and had weakly luteinized cells, he descriptively called them luteinized thecomas associated with sclerosing peritonitis. This lesion rather quickly became somewhat controversial with regard to its exact nature because some authorities felt it was not a neoplasm, but rather a peculiar non-neoplastic proliferation with some relationship to processes in the massive edema–fibromatosis family. We have discussed this issue in detail elsewhere\textsuperscript{143} and will not belabor it here, but in our second article on this topic, we included the word “thecomatosis” in parenthesis as an alternative name for this peculiar ovarian mass. Whatever name is elected, these tumors have very distinctive clinical and histologic features.

They can occur at any age (from 10 months to 85 years), but usually occur in young women (median age = 27 years), who present with abdominal pain and ascites, frequently accompanied by bowel obstruction. Rare ovarian lesions similar to those associated with sclerosing peritonitis are seen in the absence of the peritoneal process. The ovaries range from normal in size to very large, and the smaller ones often show an exaggerated cerebriform appearance. Marked edema, cyst formation, and hemorrhage are common gross findings as is a beefy-tan appearance (Fig. 21). Histologically, the cerebriform appearance that is sometimes recognizable grossly may be seen (Fig. 22) with, in some cases, sparing of the medulla. The tumors show an admixture of spindled cells and weakly luteinized cells. The spindled cells are bland cytologically, but mitotic activity ranges from minimal to extremely high. Edema is common (Fig. 23) and in many cases separates the spindled cells, imparting a microcystic appearance.

Entrapped normal ovarian elements, such as follicles and corpora albicantia, are frequently encountered. The luteinized cells stain for sex cord-stromal markers (inhibin, calretinin, and CD56); the spindle cells are generally negative, but often stain with desmin and SMA, and in many cases weakly to moderately for ER and PR.

The associated sclerosing peritonitis consists of a diffuse proliferation of spindled cells, most likely submesothelial myofibroblasts. This process can be subtle and only detected histologically, or can be massive, and mistaken for peritoneal carcinomatosis. While it usually resolves following bilateral salpingo-oophorectomy, the sclerosing peritonitis can be progressive (even after removal of the ovaries) and has led to death in rare patients and significant ongoing morbidity in some others. The ovarian lesions have not metastasized.

Differential diagnosis

This is discussed in detail elsewhere\textsuperscript{143} and includes typical luteinized stromal neoplasms (usually unilateral, sometimes hormone-producing, with large nests of luteinized cells and...
no entrapped normal elements), massive ovarian edema/fibromatosis (both much less cellular and more uniform in appearance), and occasionally other spindle-cell lesions, such as even fibrosarcoma (because of typical brisk mitotic activity) if luteinized cells are difficult to identify.

**Microcystic stromal tumor**

This is another recently defined entity (Figs. 24–27) likely in the stromal tumor category and, to date, benign. A total of 16 cases were described in adults from 26 to 63 years of age. Three patients were in their 20s. The tumors are typically solid and cystic, tan–white, and average 9 cm. They have three components: small, round-to-oval microcysts that sometimes coalesce into channels (Figs. 24 and 26), solid cellular regions (Fig. 25) with features somewhat similar to thecomas, and fibrous stroma often exhibiting hyaline plaques (Fig. 27). The cells frequently contain vacuoles and have pale to eosinophilic cytoplasm and overall bland cytology with rare mitoses, but bizarre atypia is seen in many cases. The tumors are positive for vimentin and CD10 and negative for inhibin and calretinin. They may be focally positive for keratin but are negative for EMA. It has recently been shown that these tumors may exhibit nuclear staining by beta-catenin immunohistochemistry, and this is frequently associated with beta-catenin mutations. The initial observations by Maeda et al. have been followed up in evaluation of the material from our files, and all 12 tumors stained have shown similar immunohistochemical staining results (Irving JA, manuscript in preparation, 2014).

**Differential diagnosis**

The neoplasms most realistically in the differential diagnosis are thecoma and steroid cell tumor. A thecoma is often suggested because of the hyaline plaques, but the microcystic morphology rules out thecoma, and in the cellular regions, there are cells with eosinophilic cytoplasm contrasting with the typical pale gray cytoplasm of the usual thecoma cell. Steroid cell tumor is essentially excluded, also, by the microcystic pattern, cellular regions in isolation being quite similar to steroid cell tumor. Potentially the microcystic regions could be confused with the reticular pattern of yolk sac tumor, but other differences are major. We have seen one rare case of struma ovarii that initially was confused with microcystic stromal tumor. Minor foci of typical struma and immunostains were helpful in that case.

**Thecoma**

We consider this neoplasm briefly as it is usually seen in the postmenopausal patient and has been discussed in detail recently. It has generally been stated that less than 10% of these tumors occur in the first three decades, but in our recent series, the number in this period was 20%. This figure may be skewed, because it was based on referral material, which tends to select for unusual cases, including thecomas with calcification (Fig. 28), which have a tendency to occur in the young. No thecomas in our series occurred in the first decade. Like all sex cord-stromal tumors, thecomas can rarely exhibit bizarre nuclei, and like other stromal tumors, they can exhibit very
minor sex cord elements that can be discounted from the viewpoint of prognostic significance. Tumors with calcification show adipose metaplasia in some cases. The designation luteinized thecoma has been used for either fibromas or thecomas with lutein cells, but there has been a recent trend to simply mention luteinization within fibromas, or thecomas for that matter, and a trend away from the term “luteinized thecoma.” As with any ovarian tumor having a significant number of lutein cells, stromal tumors with such are more likely to be androgenic than non-luteinized lesions. In the largest series of so-called luteinized thecomas, more of them (about 30%) occurred in the first three decades than did usual thecomas.

Differential diagnosis
Thecomas are distinguished from fibromas on the basis of their more rounded cells with abundant pale gray cytoplasm. The fibroma–thecoma family forms a spectrum, and it is perfectly appropriate to use designations such as “fibrothecoma” for neoplasms that are in part one and in part the other morphology, although we tend to use the designation of the most dominant picture. The cytoplasmic features of thecoma are in marked contrast to the luxuriant eosinophilic cells of many steroid cell tumors or, alternatively, the pale lipid-rich cells seen in some other steroid cell tumors. The most vexing differential in our experience is between a thecoma and a granulosa cell tumor with a significant thecomatous component and subtle granulosa cell neoplasia. A subset of granulosa cell tumors is strikingly thecomatous, and regions in which the cells have less cytoplasm and show subtle evidence of epithelial differentiation can be crucial to appreciate in arriving at the diagnosis of a granulosa cell tumor. Reticulin stains can be helpful in disclosing the granulosa elements.

Fibroma
Fibromas represent 4% of all ovarian tumors and are by far the most common of the stromal tumors (Fig. 29). In the classic report on ovarian fibromas from the Mayo Clinic, 2 of 283 tumors occurred in the second decade and 19 in the third decade. Cellular fibromas may also occur in the young, but are similarly uncommon. There is nothing unique to the morphology and differential diagnosis of these tumors when occurring in the young, except the following. One subset of fibromas, those associated with the basal cell nevus (Gorlin’s) syndrome typically occur in young patients and are often bilateral and calcified. The pathologist noting these particular features may occasionally lead to the syndrome being uncovered.

Signet ring-stromal tumor
This is an extremely rare tumor. The first reported case occurred in a 28-year-old, and one of the small number of additional reported tumors occurred in a 21-year-old. Varying numbers of signet ring cells are seen in a background that at first glance resembles somewhat cellular fibroma, but the cells are less spindled with less collagen production. Similar signet ring cells have been seen in some granulosa cell tumors, so thorough sampling is necessary in a tumor suspected to be a signet ring-stromal tumor. The signet ring cells have bland nuclei, and the vacuoles do not stain for...
mucin, which helps distinguish this tumor from its major differential diagnostic consideration, the Krukenberg tumor, which is usually bilateral and almost always displays epithelial elements other than signet ring cells.

**Myxoma**

These tumors are sometimes placed with the miscellaneous ovarian tumors, but as a stromal origin is likely for many of them, they are considered at this point. These exceptionally uncommon tumors have been nonfunctioning without any distinctive clinical presentation. In Dr. Scully’s series of eight cases, three patients were in the first three decades (16, 19, and 25 years of age), indicating a tendency for this neoplasm to occur in young patients, particularly as the oldest patient was 45 years. They are often sizeable, with a mean diameter of 11 cm, and typically soft and gelatinous with focal cystic degeneration. Microscopic examination shows the typical morphology as seen in the soft tissues, with widely dispersed stellate tumor cells, some with tapering cytoplasmic processes, set in a prominent myxoid stroma. The latter stains with colloidal iron and Alcian blue and is sensitive to pretreatment with hyaluronidase.

**Differential diagnosis**

As in the soft tissues, care must be taken to distinguish this neoplasm from low-grade sarcomas with deceptively benign regions. Attention to focal areas, which may be limited, of hypercellularity with modest atypia and mitotic activity is crucial. Somewhat more common, although less important, is distinguishing a pure myxoma from another stromal tumor with extensive myxoid change, such as a sclerosing stromal tumor. That some sclerosing stromal tumors, as noted earlier, can be myxoid has prompted some to consider the myxoma basically a myxoid sclerosing stromal tumor or, for that matter, other neoplasm in the thecoma-fibroma group. As a practical matter, if minor foci of more usual stromal neoplasia are encountered, the neoplasm should be classified in such a group, with a comment on the predominant myxoid change. Of course, thorough sampling is warranted in any case of putative myxoma, not only for this distinction, academic though it may be, but also for the more important one of excluding low-grade myxoid sarcoma.

**Steroid cell tumors**

These tumors are placed at this juncture because it is likely that the majority of them have a stromal origin. One subset, the Leydig cell tumor, is almost invariably a tumor of the older female, peaking in the early 60s, and is not considered here other than to note a recent report of a virilizing hilar cell tumor in a 22-year-old with the Carney complex. Although the so-called stromal luteoma is no longer considered separately in the WHO classification of steroid cell tumors, one argument for the opposite approach is that it also usually is seen at an older age than patients with steroid cell tumors not otherwise specified (NOS). Only one patient with stromal luteoma in Dr. Scully’s series, a 28-year-old, was in the span of years of interest to us here. The commonest form of steroid cell tumor, which is placed in the so-called not otherwise specified category, occurs at a younger age than the other subtypes with a mean age of 43 years, and a measurable number of them occur in the first three decades including even children in whom they are a rare cause of androgenic manifestations, sometimes even striking virilization. Isosexual pseudoprecocity, or even Cushing’s syndrome. In the largest series of these tumors, the youngest patient was two and half years of age. The specific breakdown per decade is not provided in that report, but perhaps about 20% of these tumors occur in the first three decades. In another series, the average age was higher (56 years), with the youngest patient being 16 years old.

The gross and microscopic appearances of steroid cell tumors are relatively straightforward. They are typically solid and yellow (Fig. 30), but they may be brown to almost black. Microscopic examination shows variable components of large, pale, lipid-rich cells or alternatively somewhat smaller cells with appreciable eosinophilic cytoplasm. Some single cells may be seen. One unusual tumor in a 21-year-old had a component of myelolipoma. The broad differential diagnosis of clear and oxyphil cells of the ovary may pertain, as considered in detail elsewhere. There are no unique pathologic features of these neoplasms in the young.

**Adult granulosa cell tumor**

This designation refers to the familiar form of granulosa cell tumor peaking in the early part of the sixth decade (average age 53 years) and classically presenting with bleeding around the time of the menopause or just thereafter. When Dr. Scully and I conducted a review of the many large studies in the literature as of the early 1980s, we obtained the breakdown below for the age distribution of the granulosa cell tumor. As most of those studies were conducted before the juvenile granulosa cell tumor was segregated, it must be noted that the figures pertain to all granulosa cell tumors, but as the adult form dwarfs the juvenile form in frequency, the following figures are probably more or less accurate for the frequency of the adult granulosa cell tumor in the various decades: first decade (2%), second decade (2%), third decade...
fourth decade (14%), fifth decade (26%), sixth decade (26%), seventh decade (19%), and 7% for the remaining decades. The features of these tumors are well known and have been elaborated in numerous sources so will not be discussed in detail here, but only selected comments are made.

It should be noted that the designation “adult” granulosa cell tumor was proposed shortly after the designation “juvenile” granulosa cell tumor was instituted to capture the subset of tumors occurring preferentially in young patients (see below) and with particular features. However, although these terms are convenient, they can be misleading and one has to remember occasional typical examples of the “adult” tumor occurrence in young patients (Fig. 33). They have no difference in the young and, like the juvenile form, if they occur in the prepubertal years, they may be associated with isosexual pseudoprecocity. Three of 32 granulosa cell tumors of the ovary in girls aged 16 years or younger reported from the Armed Forces Institute of Pathology were considered typical adult granulosa cell tumors.165 Three other tumors that were cystic appear to have been of uncertain subclassification, and we have found it difficult in some cases of cystic granulosa cell tumor to make the distinction between adult and juvenile forms. Our own experience suggests that cystic adult granulosa cell tumors may have a tendency to occur in the young. In our report of androgenic granulosa cell tumors, 10 patients with cystic tumors ranged from 15 to 28 years of age,166 which is distinctly younger than the age of adult granulosa cell tumors overall. In that series, the 12 patients with more typical solid or solid and cystic adult granulosa cell tumors were at an average age of 37 years, and although the specific breakdown is not available to us at this time, the youngest patient was 20 years, and the overall average age was 37 years, suggesting that a few other patients may have been under 30 years. Of the four luteinized adult granulosa cell tumors we reported, one was in a 22-year-old.167

Juvenile granulosa cell tumor

Dr. Scully became alerted to this neoplasm in the late 1960s to early 1970s when he noted that in young females, granulosa cell tumors often had alarming microscopic features. Although these atypical features are occasionally observed in older women, their strong predilection for young females led to his designating them juvenile granulosa cell tumors (JGCTs). Although the features of this tumor are now well known and covered in many sources, because this neoplasm is one of the most distinctive tumors of the ovary in the young, they merit detailed discussion here. In the Boston Children’s Hospital experience, these tumors were exactly twice as common as Sertoli–Leydig cell tumors and there were no adult granulosa cell tumors.2 Most of these do occur in juveniles, but about 3% are seen beyond 30 years of age.168 As with the adult granulosa cell tumor, the presentation is variable and in part related to the age of the patient, those seen in prepubertal girls typically presenting with isosexual pseudoprecocity, whereas those seen in the reproductive years may present with a variety of menstrual abnormalities.168,169 At either age there may be no

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Fig. 30 – Steroid cell tumor. Note the exquisite yellow color.

Fig. 31 – Steroid cell tumor, not otherwise specified. Typical cells with eosinophilic cytoplasm.

Fig. 32 – Steroid cell tumor, not otherwise specified. Sometimes there is a prominent stroma and growth of the tumor cells in the form of irregular nests and cords.
endocrine manifestations, but rather presentation in the form of abdominal swelling and pain, as seen with any sizable adnexal mass. As with the adult neoplasm, hemoperitoneum may occur. Occasional tumors occur in patients with Ollier’s disease or Maffucci’s syndrome. The tumors are usually large and range from uniformly solid and yellow to solid and cystic (Fig. 34) to dominantly cystic, a spectrum similar to that seen with the more common adult tumor. Some tumors are strikingly hemorrhagic (Fig. 35).

It is at the microscopic level that this tumor has a variety of differences that make it a unique entity and usually quite different in appearance from the adult-type neoplasm. There are typically diffuse sheets or nodules of cells with most often abundant eosinophilic cytoplasm interrupted to varying degrees by follicles (Fig. 36). The follicles may be round to oval but more typically vary in shape and size and often contain mucicarminophilic, eosinophilic, or basophilic material. Occasional tumors are prominently nodular with no or minimal follicular differentiation (Fig. 37). In the solid regions, the cells may grow as small clusters. The nuclei of the granulosa cells appear more immature than those in the adult type of tumor. They are more hyperchromatic and frequently exhibit considerable mitotic activity; nuclear grooves are rare. Up to 15% of the tumors show marked nuclear atypia. It is worth emphasizing that not all JGCTs show the characteristic abundant eosinophilic cytoplasm, and these cases may be particularly challenging (Fig. 38). Although it was a constellation of findings, both architectural and cytologic related to the nuclear features and the cytoplasm, that first prompted Dr. Scully to recognize this neoplasm, he always stressed that it was the nuclear immaturity and mitotic activity that were the most striking feature that first caught his attention.

**Differential diagnosis**

The major differences between the adult and juvenile forms of granulosa cell tumor are cytologic, specifically the hyperchromatic, mitotically active nuclei without grooves in the juvenile form. Another important difference is the typical luteinization of the cells in the juvenile tumor. In adult granulosa cell tumors, one may see luteinized cells, but they are usually a minor component and only very rare tumors in this category are extensively luteinized. Finally, the nature of the follicles in the JGCT differs in many cases from those in the adult form of neoplasm in that they exhibit much more variability in size and shape. Occasional granulosa cell tumors have both adult and juvenile features.

As malignant germ cell tumors are common in the age group in which the JGCT is most often encountered, and may even be functioning, the immature nuclei of the JGCT may lead to the misdiagnosis of a yolk sac tumor or embryonal carcinoma. However, the follicle formation that is seen at least focally in the great majority of JGCTs is diagnostic with one caveat, as noted earlier. Cysts in the polyvesicular

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Fig. 33 – Adult granulosa cell tumor. Prominent hemorrhagic appearance is seen.

Fig. 34 – Juvenile granulosa cell tumor. The tumor is predominantly solid with focal cysts.

Fig. 35 – Juvenile granulosa cell tumor. The sectioned surface is solid and cystic with focal hemorrhage.
vitelline variant of yolk sac tumor can potentially be misconstrued as cystic follicles of a JGCT. Cellular stroma between the cysts of the polyvesicular tumor and foci of typical yolk sac tumor both may be helpful. Paradoxically, the extreme nuclear atypia of some JGCTs exceeds that of the usual yolk sac tumor.

The JGCT is sometimes misinterpreted as a thecoma because of the absence or rarity of follicles, the usually abundant cytoplasm, and the occasional conspicuous theca cells. Thorough sampling to demonstrate follicles and the performance of reticulum staining to help recognize the granulosa cell nature of at least some of the tumor cells are important in establishing the diagnosis. Also, thecomas lack significant mitotic activity in almost all the cases and rarely occur in children. An important differential diagnosis is with the small cell carcinoma of hypercalcemic type, an issue discussed under the latter.

JGCTs with marked atypia may be misinterpreted as undifferentiated carcinomas if foci of follicle differentiation are overlooked. The problem that may arise most often is confusion with small cell carcinoma of hypercalcemic type, because it treacherously also has follicles whose absence generally aids in the distinction of JGCT from conventional undifferentiated carcinoma. The small cell carcinoma differential is discussed under that heading. In some cases, the tubulocystic variant of clear cell carcinoma is suggested when the follicles are lined by cells with features of hobnail cells. The absence of other patterns of clear cell carcinoma, the young age of the patient, the presence of follicles, and focal areas of more typical JGCT should help resolve this problem. In some JGCTs a pseudopapillary appearance may be encountered, leading to a superficial resemblance to transitional cell carcinoma.170 Small follicles in the lining at the base of the pseudopapillae exclude transitional cell carcinoma, and the latter is a tumor of a much older patient in most cases. A metastatic tumor that may be confused with a JGCT is malignant melanoma, because in some of the latter neoplasms, follicle-like spaces lined by cells with abundant eosinophilic cytoplasm impart a striking resemblance to a JGCT. Basophilic mucicarminophilic fluid, often present in the follicles of JGCTs, is absent in the spaces of metastatic melanoma. When the diagnosis of JGCT is being considered in a patient over 20 years of age, the diagnosis of malignant melanoma should be excluded if the putative JGCT is in any way unusual, particularly if bilateral. Immunohistochemical staining and electron microscopic examination should establish the diagnosis if other clinical and routine pathologic features do not.

**Sertoli cell tumor**

Although they may be seen at any age, Sertoli cell tumors have some tendency to occur in the young, with about one-third seen in the first two decades, and dramatic examples associated with isosexual pseudoprecocity have been reported. Virilization is seen in some other cases. In our series of 54 patients, 11 had estrogenic and four androgenic manifestations; one-third of the patients were in the first three decades, most of those being in the first two.171 About
25% of the tumors are seen in the perimenopausal and postmenopausal years. Occasionally, patients, six in our series, have Peutz-Jeghers syndrome. This includes patients with the lipid-rich variant of Sertoli cell tumor and at least two with oxyphilic Sertoli cell tumors.\textsuperscript{172–174} Two unique ovarian sex cord tumors associated with Peutz-Jeghers syndrome, each responsible for sexual precocity, occurred in the first decade.\textsuperscript{175} These are probably best considered unclassified sex cord tumors, but it is simplest to mention them here.

Sertoli cell tumors are typically unilateral, are usually 5–12 cm, solid, yellow, and are often lobulated (Fig. 39). The microscopic features have been described in detail relatively recently,\textsuperscript{171} so they are not elaborated here, particularly as there are no differences in the young other than perhaps a tendency for the lipid-rich form to occur in them. As has been stressed recently in the testis, so also in the ovary, one may see a septal framework with lymphocytes resulting in the formation of an alveolar to nested pattern (Fig. 40), which on low power may be vaguely reminiscent of the pattern of dysgerminoma, but there are numerous differences between those two neoplasms that will help distinguish them. With regard to the differential diagnosis, also discussed in detail elsewhere, we will simply reiterate that this is a diagnosis of exclusion as so many tumors may mimic Sertoli cell tumors to a degree. However, most of the latter will show some morphology in well-sampled neoplasms that excludes Sertoli cell tumor, and immunochemistry may play a role in this differential diagnosis.

**Sertoli-Leydig cell tumors**

Sertoli-Leydig cell tumors (SLCTs) tend to occur in young females. In our large series, 6% occurred in the first decade, 46% in the second, and 23% in the third.\textsuperscript{176} Only about 10% arise after 50 years of age.\textsuperscript{176} SLCTs may be well differentiated, of intermediate differentiation, or poorly differentiated, and each of the latter two may have heterologous and/or retiform elements.\textsuperscript{176–178} Those that are well differentiated occur on average about a decade later than the tumors overall (35 years versus 25 years). Overall, about 50% are androgenic, but the figure is only 25% for retiform tumors and about 40% for tumors with heterologous elements. We begin with perhaps the most intriguing subtype and certainly the one with a particular tendency to occur in the young (average age 15 years), the retiform variant,\textsuperscript{179–181} which predominates in about 10% of SLCTs.

Retiform SLCTs are characterized by microscopic growth patterns that simulate those of the rete testis. They are grossly often soft and spongy or cystic with edematous intraluminal polypoid excrences. The basic microscopic pattern is an irregular network of elongated, often slit-like, tubules (Fig. 41) and cysts that often contain papillae. The papillae may be short and rounded or blunt, often containing hyalinized cores, or larger with fibrous or edematous cores (Fig. 42). In other instances, they are cellular and quite reminiscent of a serous papillary tumor (Fig. 43). Cysts may be markedly dilated with eosiinophilic secretion in some cases. The tubules are usually lined by a single layer of cuboidal epithelial cells with round-to-oval nuclei, although stratification is conspicuous in some cases. The cytoplasm is typically scanty and mitotic activity is variable, but sometimes marked. Similar cells typically line the papillae and cysts, but large cysts may be lined by flattened cells. The stromal component varies from moderately cellular fibrous tissue to markedly edematous (accounting for the soft, spongy consistency) to very cellular, immature mesenchymal tissue, which may show heterologous differentiation.

Non-retiform tumors are typically solid, yellow, lobulated neoplasms (Fig. 44), but in some instances they are strikingly cystic. Overall, the solid and cystic appearance, with hemorrhage within cysts, that is characteristic of the granulosa cell tumor is less common, but may be seen occasionally. Sometimes the cysts contain a watery fluid. In tumors with heterologous mucinous elements\textsuperscript{182} a component of the tumor may be indistinguishable from a mucinous cystic neoplasm. Tumors with mesenchymal heterologous elements\textsuperscript{183} tend to have a nonspecific malignant-appearing sectioned surface with hemorrhage and necrosis, in accord with the fact that most such tumors are poorly differentiated.

Microscopic examination of well-differentiated tumors typically shows a uniform tubular pattern. The tubules are separated by stroma usually containing copious Leydig cells.
The tubules are typically overtly Sertoliform in morphology but confusion can be caused by an occasional case in which they appear endometrioid-like. The breadth of morphology of the tumors of intermediate differentiation is quite remarkable (Figs. 45–51). Most typical on low power and probably accounting for the appearance of about 80% of the tumors is growth in the form of densely cellular “blue” lobules composed predominately of Sertoli cells with scant cytoplasm but punctuated to a degree by Leydig cells. Leydig cells are generally more conspicuous in the interlobular areas that are often edematous. Within the lobules, the Sertoli cells may grow diffusely but more typically grow in vague alveolar formations, but essentially any epithelial arrangement may be encountered. Growth of both Sertoli cells and Leydig cells as cords may be conspicuous, particularly at the periphery of lobules. A confusing feature of some tumors is the presence of microcysts or even macrocysts. The former may superficially resemble to a limited degree the reticular pattern of yolk sac tumor and the latter sometimes contain eosinophilic secretion that may appear thyroid-like. Tumors that are not poorly differentiated may contain bizarre nuclei (Fig. 51) that may result in erroneous categorization as poorly differentiated. Poorly differentiated tumors are only recognizable as being SLTCs when they have some, albeit often minor, component of clear-cut Sertoli differentiation. Such tumors are usually composed predominately of a sarcomatoid pattern of malignant cells with brisk mitotic activity, although sometimes a solid carcinoma-like pattern may be encountered. Rarely the cells have a particularly primitive appearance and in isolation can be somewhat reminiscent of embryonal carcinoma.

The heterologous mucinous epithelium, which is seen in about 20% of all SLTCs (Figs. 52 and 53), is typically composed of randomly arranged mucinous glands and cysts of intestinal type, punctuating the tumor, but some neoplasms have foci that independently are purely mucinous and potentially at, for example, frozen section can cause confusion if they alone are sampled. The neuroendocrine cells that are a component of the intestinal-type epithelium often give rise to small foci of carcinoid, which only exceptionally form a grossly evident nodule. The carcinoid may be in the form of typical insular carcinoid but more often forms small little aggregates of cells with eosinophilic cytoplasm, sometimes potentially being misconstrued as Leydig cells, and occasionally with goblet cells, resulting in a goblet cell carcinoid-like morphology. Yet another eosinophilic cell type differentiated.

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**Fig. 41 – Retiform Sertoli–Leydig cell tumor.** The typical slit-like appearance of tubules.

**Fig. 42 – Retiform Sertoli–Leydig cell tumor.** Edematous polypoid formations and cellular papillae are seen.

**Fig. 43 – Retiform Sertoli–Leydig cell tumor.** The appearance of a serous papillary tumor is simulated.

**Fig. 44 – Sertoli–Leydig cell tumor.** The tumor is mostly solid, but has focal cysts.
Fig. 45 – Sertoli–Leydig cell tumor of intermediate differentiation. Typical low-power appearance of densely cellular lobules dominated by darkly staining Sertoli cells.

Fig. 46 – Sertoli–Leydig cell tumor of intermediate differentiation. Aggregates of Leydig cells are present and additionally an acinus is consistent with a canaliculus of hepatic type.

Fig. 47 – Sertoli–Leydig cell tumor of intermediate differentiation. Jumbled admixture of darkly staining Sertoli cells and Leydig cells with copious eosinophilic cytoplasm.

Fig. 48 – Sertoli–Leydig cell tumor of intermediate differentiation. Alveolar pattern is seen.

Fig. 49 – Sertoli–Leydig cell tumor of intermediate differentiation. Growth in the form of cords is conspicuous, and some small Sertoli tubules are seen.

Fig. 50 – Sertoli–Leydig cell tumor of intermediate differentiation. Sertoli tubules punctuate a background of predominant Sertoli cells with scant cytoplasm and occasional Leydig cells with vacuolated cytoplasm.
in SLCTs, but a rare one, is a hepatoid cell, rarely even forming canaliculi (Fig. 46). Heterologous mesenchymal elements\textsuperscript{183} that are seen in about 5% of SLTCs consist of foci of embryonal rhabdomyosarcoma (Fig. 54) or chondrosarcoma. These components are typically seen in poorly differentiated tumors and probably have a slightly adverse impact on prognosis, particularly when there is a skeletal muscle component. The extent of these components is variable, and small foci may be overlooked.

**Differential diagnosis**

Retiform SLCTs may cause diverse problems. Because of the young age of the patient and presence of papillae in many cases, the diagnosis of yolk sac tumor is often considered. It should be remembered that like many ovarian tumors, the retiform SLCT may contain hyaline bodies. A resemblance to a serous borderline tumor may be imparted by the presence of small papillary clusters in the cyst lumens. The clefts, papillae, and a complex branching pattern associated with cellular stratification and atypicality may suggest serous adenocarcinoma. In the original description of this entity,\textsuperscript{179} two cited cases are definite or probable retiform SLCT reported as serous neoplasms. The admixture of retiform tubules with immature mesenchymal tissue, which may show heterologous differentiation, can suggest the diagnosis of a malignant mixed mesodermal tumor. The presence of typical foci of SLCT in most cases, although sometimes very small in amount, and other clinical and pathologic features of the tumors should enable the diagnosis of a retiform SLCT to be established. Any pattern of SLCT may co-exist with the retiform pattern, but typically, the retiform foci merge with long, thick ribbons of immature cells consistent with Sertoli cells. When a tumor is entirely retiform, knowledge of the existence of this distinctive subtype of SLCT is essential in enabling the pathologist to avoid a serious error in diagnosis.

Many neoplasms can enter into the differential diagnosis of non-retiform SLCTs. The first of these is the granulosa cell tumor, although generally, typical forms of each category are

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**Fig. 51 – Sertoli–Leydig cell tumor of intermediate differentiation. Bizarre nuclei are conspicuous and can result in the diagnosis of a much more ominous neoplasm.**

**Fig. 52 – Sertoli–Leydig cell tumor with heterologous elements. Mucinous glands on background of typical Sertoli–Leydig cell neoplasia are seen.**

**Fig. 53 – Sertoli–Leydig cell tumor with heterologous elements. The typical appearance of mucinous epithelium.**

**Fig. 54 – Sertoli–Leydig cell tumor with heterologous elements (rhabdomyosarcoma). Islands of primitive mesenchymal cells, some of which on high power could be determined to be rhabdomyoblasts, within edematous stroma.**
easily distinguished. As with the spectrum in the fibroma-thecoma family, one has to acknowledge that in the sex cord-stromal family, there are cases that “straddle the fence.” However, they are unusual, and the distinctive lobulation of the majority of SLCTs is in contrast to the more diffuse growth that typifies the majority of adult granulosa cell tumors. Juvenile granulosa cell tumor versus SLCT should be rarely a significant diagnostic issue. As the reader will well know, there is a time-honored designation, “gynandroblastoma,” which has been used over the years for tumors that have components of note of more than one typical sex cord type (Fig. 55). During the years I worked with him, Dr. Scully gradually grew to dislike this term, because he felt it did not convey much information to most clinicians who might not be familiar with the designation and felt that it was better to consider tumors with two patterns, or potentially even three, sex cord-stromal tumors of mixed type with a clear indication of what subtypes were present, analogous to the approach to mixed germ cell tumors of the gonads. Truly minor foci of one form in a tumor dominantly of another form do not merit recording. For example, one occasionally sees in SLCT minor foci of follicle differentiation that out of context would fit better for a JGCT. The differential diagnosis with tubular Krukenberg tumor is discussed in the section on metastatic tumors. SLCTs from pregnant patients (see below) may have loose edematous regions somewhat reminiscent of reticular yolk sac tumor, but other foci should aid in the differential.

The high grade of some poorly differentiated SLCTs, and their sarcomatoid morphology, may make a pure sarcoma a consideration. Thorough sampling to identify sex cord elements is crucial. The rare differential diagnosis with a malignant mixed mesodermal tumor is aided by appreciating that the epithelial components of that tumor and Sertoli–Leydig cell tumors are usually markedly different, although the potential for a retiform neoplasm to mimic a serous component of a malignant mixed tumor certainly exists. In general, the overall components of the two tumors should be sufficiently different such that they can be distinguished.

**Sex cord tumor with annular tubules**

This morphologically distinctive pattern of sex cord-stromal neoplasia, first recognized by Dr. Scully in his article in 1970,185 may be associated with Peutz–Jeghers syndrome or seen in its absence. In a review of 27 Peutz–Jeghers-associated cases, it is noteworthy that 16 of the cases were identified in the first three decades, including two children in the first decade.186 The tumors occurring in the absence of the syndrome occur at a slightly older age group but, as suggested by a mean age of 34 years, can be seen in the first three decades. The distinctive differences in the two settings are well known, as is their morphology.

**Differential diagnosis**

The relatively uniform rounded formations of this lesion are very reminiscent on low power of the formations of gonadoblastoma, but the clinical setting is usually markedly different, and germ cells are absent in the sex cord tumor. Overlap has to be acknowledged in some cases with granulosa cell tumor and Sertoli cell tumor, but the very particular annular tubular morphology of the lesion being considered here is different from Call–Exner bodies and is generally different from the usual patterns of Sertoli cell neoplasia. Tumors in the next category considered may have an annular tubular pattern, but the finding of germ cells moves them into that group.

**Mixed germ cell-sex cord-stromal tumors, unclassified**

As these tumors contain both germ cell and sex cord elements, their discussion at this juncture is appropriate, and rare though they are, they typically occur in young girls in the first decade.187–191 They were first separated out convincingly by Talerman as a neoplasm that, like the gonadoblastoma, has sex cord and germ cell elements, but unlike the gonadoblastoma, does not have an association with abnormal sexual development, and the karyotype is normal. Occasional tumors have been clinically dramatic because of isosexual pseudoprecocity. One tumor was bilateral, but its gross features do not appear to have been distinctive. They have a more heterogeneous microscopic appearance than does the gonadoblastoma, growing in solid aggregates, broad cords, and sometimes solid tubules. A pattern reminiscent of that of the sex cord tumor with annular tubules has been described,186 as has a retiform pattern.190 In contrast to gonadoblastoma, hyaline material and calcification are either absent or unimpressive. Two tumors contained what was considered by some a surface epithelial component, and in one, glands and cysts were lined by mucinous epithelium of intestinal type.191 Although our own personal experience with the neoplasm in the ovary is limited, we believe that ovarian examples stand up better to close scrutiny than do testicular ones.

**Fig. 55 – Sex cord-stromal tumor of mixed types. There are components of adult (center) and juvenile (right) granulosa cell tumor, and well-differentiated Sertoli cell tumor (left).**
Miscellaneous primary ovarian tumors

Miscellaneous primary ovarian tumors are considered before the familiar surface epithelial neoplasms because it is within this category that one sees one of the most distinctive of all ovarian tumors of the young, the neoplasm now discussed.

Small cell carcinoma of ovary, hypercalcemic type

This is the most common form of undifferentiated ovarian carcinoma in women under 40 years of age.\(^{192}\) It was recognized by Dr. Scully in the early 1970s and was first presented in detail by him in his first fascicle. It was the unusual occurrence in young women of a small cell carcinoma that was associated with paraneoplastic hypercalcemia that led it to being recognized as a distinct entity. The patients have ranged from 14 months to 43 (mean = 24) years of age. It is rare in the first decade.\(^ {193}\) Most patients present with signs and symptoms related to an abdominal or pelvic mass, but rarely, the clinical presentation is related to the hypercalcemia. Occasional familial cases have been encountered. In the largest series, the stage was IA in 33%, IB in 1%, IC in 16%, II in 5%, III in 43%, and stage IV in 1%. This carcinoma has a dismal prognosis. The overall survival rate is approximately 16%; the corresponding figures are 33% for stage 1A tumors and 7% for tumors >stage 1A. Favorable prognostic factors have included an age <30 years, a normal preoperative serum calcium, bilateral oophorectomy, tumors <10 cm, no large cell component, and the administration of adjuvant radiotherapy. No chemotherapy has proven to be of significant consistent benefit in the management of patients with this highly malignant tumor. Recent molecular investigations have identified SMARCA4 gene mutations,\(^ {194-196}\) which has suggested to some a relationship of the hypercalcemic neoplasm with atypical teratoma/rhabdoid tumor and malignant rhabdoid tumor, but the implications of this finding remain to be fully elucidated.

The tumors are almost always unilateral, usually large, solid, soft, and white. This is similar to dysgerminoma and lymphoma and may contribute to confusion with these neoplasms as considered below. Necrosis and hemorrhage are conspicuous in many cases. On microscopic examination, the most common pattern is a more or less diffuse arrangement of small, closely packed cells with scant cytoplasm (Fig. 56), but evidence of their epithelial nature is provided by the focal presence of small nests (Fig. 57), cords, and clusters of cells. An important feature that is seen in about 80% of the tumors is follicles (Fig. 58) that vary from small to large, more often the latter. They are usually round to oval and contain eosinophilic fluid. The tumor cells have small nuclei containing a single nucleoli and, despite the aggressive nature of this tumor, are relatively monotonous in appearance with the exception noted below. Mitotic figures are numerous.

Variant features may be seen, which complicate the interpretation in many cases. The commonest is the presence in about half of the cases of a component of large cells with moderate to abundant eosinophilic cytoplasm (Fig. 59), referred to as the “large cell variant.” This pattern is associated in some cases with a prominent stroma, which often is myxoid. Overall, the small cell carcinoma has relatively unimpressive fibrous stroma in most cases, but it is occasionally focally relatively prominent. The large cells may have eccentric nuclei and dense globular cytoplasm. Nucleoli are usually more prominent in foci of the large cell variant. Rarely some cells have clear cytoplasm. An intriguing finding in about 10% of these tumors is minor foci of mucinous epithelium that typically stands out sharply from the background sea of small cells. Occasionally, however, the mucinous epithelium is less conspicuous and more cytologically atypical and may merge with the small cells. Rarely signet ring-type cells are seen.

Differential diagnosis

This tumor may be confused with a granulosa cell tumor of either adult or juvenile types. However, the cells of the small cell carcinoma do not have the characteristic pale, often grooved, nuclei of the adult granulosa cell tumor and the mitotic rate in the small cell carcinoma far exceeds that encountered in adult granulosa cell tumors. Distinction from the juvenile granulosa cell tumor is generally easy because the cells of the small cell carcinoma usually lack the...
abundant eosinophilic cytoplasm that is a typical feature of the cells of the juvenile granulosa cell tumor. Even in cases of the large cell variant, distinction can usually be made because such cells are most often a focal finding and, in addition, they differ in appearance from the cells of the juvenile granulosa cell tumor because of their dense, sometimes globular, cytoplasm, only rarely seen in the juvenile granulosa cell tumor. When large cells are present, it is helpful that in cases of small cell carcinoma, there is generally a much more disorderly architecture. As noted in the consideration of JGCT, not all such tumors have the typical abundant eosinophilic cytoplasm that generally is striking. JGCTs with a limited amount of cytoplasm, particularly if briskly mitotic, may make the small cell carcinoma of hypercalcemic type a realistic consideration. On high-power examination, there can be alarming similarity between individual cells of each neoplasm. As befits its highly malignant nature, there is generally a more disorderly arrangement of the epithelial elements in the small cell carcinoma compared to the JGCT. Finally, the small cell carcinoma often has spread beyond the ovary at presentation, which is unusual for either variant of granulosa cell tumor.

Because of a shared age predilection, frequent indistinguishable gross features, and the occurrence of hypercalcemia in some dysgerminomas, small cell carcinomas may be confused with dysgerminoma, as noted earlier. Although the small cell carcinoma may have fibrous stroma, it generally differs in quality from the delicate fibrous septa of the dysgerminoma, and although, like any tumor, there may be some nonspecific inflammatory cell infiltrate, the classic lymphocytic infiltrate that tends to hug the septa, typical of dysgerminoma, is lacking in the small cell carcinoma. The squared off nuclei of dysgerminoma are not seen in the small cell carcinoma, although this feature, and others for that matter, are not as overt in cases of dysgerminoma that are poorly preserved. If necessary, the typical immunostaining of dysgerminoma will be helpful.

The differential diagnosis of the small cell carcinoma is also with other small cell malignant tumors that may involve the ovaries. Only those that characteristically occur in the same age range as the small cell carcinoma will be considered here. These include primary primitive neuroectodermal tumors, metastatic neuroblastoma, malignant lymphoma and leukemia, metastatic round cell sarcomas, metastatic malignant melanoma, and the intra-abdominal desmoplastic small round cell tumor.

In cases of neuroblastoma, the presence of Homer Wright rosettes is diagnostic, although such structures may be few in number. Appreciation of fibrillar material may also be important in the diagnosis in these cases and is even more crucial in cases of the primitive neuroectodermal tumor. In the latter tumor, the cells are even smaller than in the small cell carcinoma and lack the distinctive follicles and other patterns.

The differential with lymphoma or leukemia may arise, but the typical cytologic features of the malignant lymphoid or leukemic cells differ from those of the cells of the small cell carcinoma, and the frequent follicle-like spaces of the latter are helpful in this differential. Melanoma metastatic to the ovary may be composed of small cells with scanty cytoplasm and follicle-like spaces that produce a pattern similar to that of small cell carcinoma. However, these tumors also usually contain nevoid aggregates of cells that suggest melanoma and often a noteworthy history. In cases of the intra-abdominal desmoplastic small round cell tumor, the ovarian involvement is much more often bilateral, and there are overt histologic and immunohistochemical differences. The possibility of a small cell carcinoma may be raised in cases of metastatic alveolar rhabdomyosarcoma, because the follicle-like spaces of the small cell carcinoma may be simulated by cystic changes in the alveolar spaces of the rhabdomyosarcoma. However, the distinctive and prominent alveolar pattern of rhabdomyosarcoma is not a feature of small cell carcinoma. The giant cells that are seen in some rhabdomyosarcomas have not been encountered in the hypercalcemic small cell carcinoma. Immunostains may be called upon to assist in the differential in most of the above situations. The differential diagnosis of the small cell carcinoma may also be that of a large cell malignant tumor when the tumor is
predominantly the large cell variant. This is a topic unto itself, which has been considered in detail elsewhere.164

**Wolffian tumors**

Only one of the 11 tumors in this rare category we reported some years ago was in the first three decades, in a 28-year-old.197 These tumors have no distinctive features in this age group. As in later years, their differential diagnosis with a Sertoli cell tumor of the ovary may be a challenge, but the distinctive sieve-like pattern of most wolffian tumors is a very helpful finding.

**Rete cysts (cystadenomas)**

These rare benign cystic lesions of the ovary typically occur in postmenopausal patients with a mean age of 59 years, but one patient was 23 years old.198 Rete cysts may be associated with striking peripheral luteinization,199 which may cause androgenic manifestations, although they were not present in the patient just referred to.

**Paraganglioma**

One of the reported examples of this rare ovarian tumor occurred in a 22-year-old woman.200 There were no distinctive symptoms associated with the tumor. As these neoplasms of the ovary have been reported in detail recently, they are not elaborated here.

**Solid pseudopapillary tumor of pancreatic type**

Two of the three examples of this tumor arising in the ovary that we initially reported occurred in patients aged 17 and 21 years,201 and an additional reported case occurred in a 25-year-old.202 The diffuse eosinophilic and pseudopapillary architecture (Fig. 60), which dominates in these tumors, as well as cells with vacuolated cytoplasm, may produce a broad differential diagnosis as discussed in detail elsewhere, and immunohistochemical staining for β-catenin may be helpful.

**Melanotic XP-11 tumor of renal type**

One example of this tumor has been described in the ovary of an adolescent girl.203 It was a 10-cm mass with a white-to-yellow focally myxoid sectioned surface, and microscopic examination showed nests of cells in a stroma showing calcification. The tumor cells had abundant clear cytoplasm with finely granular melanin pigment and expressed gp100 protein (recognized by the HMB-45 antibody) and tyrosine.

**Mesenchymal tumors**

The most common tumors in this group are the fibroma and cellular fibroma, but by convention, they are considered earlier with the stromal tumors. The uncommon fibrosarcoma of the ovary is typically seen in older patients, but at least one has been seen in the first decade, an unusual case, as it occurred in an 8-year-old girl with the basal cell nevus syndrome.204 As is typical of the syndrome, the fibromatous tumors in that case were bilateral, and the fibrosarcoma was considered to have arisen in preexistent fibroma. At least one other fibrosarcoma of the ovary in a young girl, a 12-year-old, has been reported.205

Sporadic examples of fibrosarcomas in the third decade may be found in occasional series of ovarian sarcomas. One fibrosarcoma in a teenager complicated Maffucci’s syndrome.206 A tumor interpreted as an “undifferentiated” sarcoma was found in a 20-year-old.207

When we reviewed the literature on rhabdomyosarcoma at the time of a previous study,7 we found that one-third of the small number of reported tumors had occurred in patients in the first two decades, including a child of 13 months. The majority of those tumors were of the pleomorphic variant, but occasional embryonal rhabdomyosarcomas had been reported as of that time.208 The largest reported experience with ovarian rhabdomyosarcoma was subsequently reported by Nielsen et al.209 Three of the 13 patients in that series were girls from 7 to 14 years of age, and three others were in their 20s. Two tumors were of alveolar type and the remainder were embryonal. Rarely, rhabdomyosarcoma may present with a clinical picture simulating that of leukemia, and at least one ovarian example of this phenomenon associated with a mixed embryonal, alveolar, and pleomorphic rhabdomyosarcoma has been described in a 16-year-old.210 Nielsen et al.211 have also reported the largest series of cases of angiosarcoma of the ovary and a notable tendency for that neoplasm to be found in the young is evident, as all seven patients were in the span of 20–32 years of age, mean 26 years. There were the typical hemorrhagic gross characteristics and microscopic features as seen in the soft tissues. One infantile hemangioendothelioma has been reported in a neonate.211 A patient with pelvic soft tissue-type fibromatosis had widespread disease, which included a 23-cm ovarian tumor.212

Smooth muscle tumors of the ovary are much less common than their uterine counterpart, and the only large series was composed mainly of consultative material.213 In that series of 54 tumors, the majority were leiomyomas, one from a child aged 3 years and one, which was myxoid, in a 19-year-old.213 They occurred overall in a somewhat youthful age group as attested to by a mean age of 38 years. A similar comment

![Fig. 60 – Solid pseudopapillary tumor of pancreatic type. The typical papillary and solid patterns are seen.](image-url)
pertains to cellular leiomyomas, which had an identical mean age, but in that group, the youngest patient was 20 years old. The youngest of the 24 patients with leiomyosarcoma was a 25-year-old. There was only one other patient under 30 years. There are no distinctive features of smooth muscle tumors of the ovary in the young. A similar comment pertains to sporadic benign soft tissue tumor of miscellaneous types occasionally seen in the ovaries of the young. A brief note is made of a few cases of bilateral ovarian hemangiomias in patients, typically in the first three decades, who have hemangiomatosis.214

Gestational trophoblastic disease

A final rare category of miscellaneous primary ovarian neoplasia is gestational trophoblastic disease. As that is one of a number of interesting and unusual aspects of ovarian masses encountered during pregnancy, it is included later in a section specifically devoted to that overall topic.

Mesothelial neoplasms

One of the small number of adenomatoid tumors of the ovary reported occurred in a 23-year-old.215 The small size and circumscription may be important in distinguishing these from the rare malignant mesothelioma that involves the ovary and may have adenomatoid-like areas. Although malignant mesothelioma, like adenomatoid tumor, is usually seen in an older age range, it is noteworthy that of the nine cases we reported presenting as ovarian masses, two of the patients with serous borderline tumors with microinvasion, the youngest patient was 17 years, the mean age 43 years, and 52% of the patients were 35 years of age or younger.224 They are exceptionally rare in the first decade, but in our prior article on this topic,7 we noted having seen serous borderline tumors in a 4-year-old and a 10-year-old and illustrated the non-invasive implants present in the younger girl. Mucinous tumors in the first decade are similarly rare, but documented. Serous carcinoma, and even more so endometrioid and clear cell carcinoma, remain distinctly uncommon even in the third decade, but cases in the teens and 20s are reported.229 In a report of 14 low-grade serous carcinomas with a micropapillary pattern, there was a 28-year-old and a 30-year-old.230 Most mucinous carcinomas in these years in our experience are low-grade carcinomas, although it does occur in a somewhat younger age group overall than does the malignant mixed mesodermal tumor of usual type. The youngest patient with adenosarcoma in our series of ovarian cases was a 30-year-old.213

Surface epithelial stromal tumors

These tumors are rare in the first decade and uncommon in the second, but they are then seen with some appreciable frequency in the third decade. As they have no special pathologic features in the young, only a few general remarks are made. Relatively few studies have specifically looked at surface epithelial neoplasms in the first three decades. A recent publication looked at the experience with tumors in patients up to 18 years of age.219 Albeit it is from a referral center which may introduce some bias, the results are of interest in as much as mucinous and serous tumors accounted for all the 69 neoplasms, indicating what is evident from the literature overall and our own personal experience, namely the rarity of any other cell type in the surface epithelial family. In that series, 37 were benign, 24 were borderline, and only three were frankly malignant. In each category, the serous tumors outnumbered the mucinous tumors, but only marginally in the borderline group, and the numbers in the carcinoma category are too small to draw meaningful conclusions. In our own experience with ovarian tumors in the young, we have found that mucinous neoplasms are more common than serous neoplasms and that is certainly so if carcinomas are considered. In a recent report of 46 mucinous carcinomas, there were four from patients younger than 30 years, but only one, a 19-year-old, was in the first two decades.220 That experience is representative of that in the literature overall, indicating that mucinous carcinomas prior to 20 years, although encountered, are rare. More common are mucinous borderline tumors in teenagers. The same group of authors published a large experience with mucinous borderline tumors, and 40 of their 171 patients were 30 years of age or less. In that group, 13 patients were aged from 13 to 20 years.221

Müllerian mucinous borderline tumors and the müllerian borderline tumors of mixed cell type (so-called seromucinous borderline tumors) also may occur in young patients. The average age in the two articles defining these tumor types was in the mid-30s, and the youngest patient in one report was 17 years and in the second was 19 years.222,223 As noted in the introductory remarks, as one moves through the 20s, serous borderline tumors become seen with some greater frequency before becoming significantly more common once a patient passes beyond 30 years. One could select many articles from the literature to make the point that serous borderline tumors are not rare in patients in the 20s and just one example is selected here. In a series of 21 patients with serous borderline tumors with microinvasion, the youngest patient was 17 years, the mean age 43 years, and 52% of the patients were 35 years of age or younger.224

Mixed mesodermal tumors

A conventional tumor in this group with frankly malignant epithelial stromal components is almost unheard of before 30 years of age, and so also is the lower grade neoplasm, the adenosarcoma, although it does occur in a somewhat younger age group overall than does the malignant mixed mesodermal tumor of usual type. The youngest patient with adenosarcoma in our series of ovarian cases was a 30-year-old.213
Metastatic tumors

As the majority of ovarian tumors that spread to the ovary are the common cancers of the middle-aged or older patient, in general, metastatic neoplasia in the ovary is less common in the first three decades compared to later life. With one or two exceptions, there are no particular unique features to these neoplasms in these years, and as the topic of metastatic tumors has been reviewed in detail in many sources recently, remarks here will be brief.

Ovarian spread may be seen from time to time, both of those neoplasms characteristic of the earlier years of life as well as some usually seen in later life but which sporadically appear in the young. For example, in a recent large study of Krukenberg tumors, four patients (3%) were in the second decade, and other similar cases are documented. In the series just noted, 17 patients (14%) were in the third decade. Other familiar causes of metastatic neoplasia in older patients, such as colorectal carcinoma, are rare in the first three decades, but may be encountered, and we have seen one in a patient as young as 12 years. In a study of 86 cases of ovarian metastasis from colorectal cancer, the youngest patient was 19 years old, and another patient was in the third decade. In our prior review, we were able to find a handful of other metastatic colorectal cancers in teenagers. When going through our reprint files, we found many series of diverse other “adult” cancers with usually no more than one case of ovarian spread in a woman under 30 years, and usually in the third decade. None of these tumors has any special feature in this age group.

In a review of metastatic ovarian tumors in children, a series of 14 cases, the age range was 14 weeks to 15 years. Eight of the tumors were neuroblastomas, most primary in the adrenal gland, but one primary in the posterior mediastinum. The other tumors were rhabdomyosarcomas of the ethmoid sinus, right occipital region, and left thigh, and individual examples of Ewing’s sarcoma, rhabdoid tumor, and a carcinoid tumor of the lung. Two other cases of alveolar rhabdomyosarcoma metastatic to the ovary in a 17-year-old and 27-year-old have been reported. Perhaps the only point in differential diagnosis worthy of comment here is one well known in pediatric pathology, that of a small round cell tumor. Of course, the clinical findings will usually aid in a differential diagnosis, but the presence of a fibrillar background in the case of neuroblastoma may also be helpful, and of course a variety of immunohistochemical techniques may aid.

Hematolymphoid neoplasms

The ovary is the most common site of female genital tract involvement by malignant lymphoma and a variety of subtypes may be encountered. Most cases of primary ovarian lymphoma consist of cases in which patients present with ovarian involvement, although staging may reveal more widespread disease. Secondary ovarian involvement by lymphomas arising in other sites is almost certainly more common than primary ovarian lymphoma. In a series of 30 cases of ovarian involvement, four had localized ovarian disease and 26 had disseminated disease. Of the four patients with localized disease, one was a 29-year-old. The youngest with disseminated disease was 21 years old. However, in a study that looked at female genital tract involvement, primary neoplasia was considered more common. In that series, 15 of 17 cases in patients under 20 years had adnexal involvement. In another series, two of 11 patients who presented with ovarian manifestations were teenagers. In another series, 14 of 40 patients were under 20 years.

One of the most important aspects of ovarian involvement by malignant lymphoma from a worldwide perspective is the frequent involvement of the organ in cases of Burkitt’s lymphoma. In parts of the world where this disease is endemic, ovarian involvement is second only to involvement of the jaw as the presenting manifestation of the disease. Specific to our interest here, in the first two decades, Burkitt’s lymphoma is by far the most common lymphoma encountered, again from the worldwide perspective. In a series from Africa, 93 of 169 ovarian tumors encountered in the first two decades were Burkitt’s lymphoma. Even when other lymphomas are considered, ovarian lymphoma in younger patients is almost always an aggressive diffuse lymphoma.

Grossly, bilateral, hilarity is common, circa 50% of the cases, and the soft, white gross appearance may be indistinguishable, as noted earlier from that of dysgerminoma or the small cell carcinoma of hypercalcemic type. The bulk of disease ranges from microscopic to large bulky masses, and microscopic features parallel those of the particular form of lymphoma, but notably, growth in the form of cords and nests is not uncommon and may lead to confusion with a number of more common ovarian tumors, such as metastatic breast carcinoma and undifferentiated carcinoma. Spindling of tumor cells, a storiform pattern, and sclerosis may even suggest sarcoma. Obviously, this is an area where immunohistochemistry has a valuable role. Although most malignant lymphomas are either Burkitt’s or diffuse large B-cell lymphomas, rare cases of anaplastic large cell lymphoma of T-cell type have been reported, including in a 16-year-old, as has B-cell and T-cell lymphoblastic lymphoma/leukemia, the latter in a 19-year-old. Involvement by Hodgkin lymphoma is rare.

Although ovarian involvement has been found at autopsy in about 10% of patients with leukemias, involvement is less common than that of lymphoma in surgical pathology specimens. In a series of 11 cases of female genital tract involvement by granulocytic sarcoma, two of the patients with ovarian disease were under 30 years of age, a 13-year-old with bilateral ovarian involvement and a 25-year-old with involvement of the right ovary. In another similar series, also of 11 cases, unilateral ovarian involvement was seen in a 17-year-old and a 25-year-old. Case reports and small series of cases of various subtypes of leukemia involving the ovary in a significant manner in the young are sporadically reported. The differential diagnosis in these cases is broadly similar to that of malignant large cell lymphoma involving the ovary, considered thoroughly by Dr. Judith A. Ferry in her book on extranodal
lymphomas, and again, immunohistochemical staining may be definitive.

**Issues related to ovarian tumors discovered during pregnancy**

As the era from menarche through the end of the third decade accounts for a significant component of the reproductive era in females, a number of ovarian neoplasms will develop, or at least be discovered, during this time in patients who are pregnant. Furthermore, pregnancy itself is responsible occasionally for the development of some specific tumor-like lesions. In this brief summary I comment on (1) tumor-like lesions specific to pregnancy, and also cystic corpus luteum in pregnancy; (2) alterations in sex cord-stromal tumors due to pregnancy, which may hinder their microscopic recognition; (3) nonspecific changes in ovarian neoplasms associated with pregnancy; (4) ovarian tumors with functioning stroma related to pregnancy; (5) gestational trophoblastic disease in the ovary; and (6) miscellaneous other aspects.

When a patient is known to be pregnant, the possibility that a mass lesion of the ovary, either cystic or solid, might be non-neoplastic should always be considered, assuming appropriate gross and microscopic findings. Otherwise, completely benign lesions may result in overly aggressive treatment with unfortunate consequences upon future fertility and increased morbidity.

Three lesions may mimic cystic neoplasms: hyperreactio luteinalis (multiple luteinized follicle cysts), the large solitary luteinized follicle cyst of pregnancy and the puerperium, and a corpus luteum cyst. It is helpful that the first lesion is bilateral in contrast to many cystic neoplasms that might be in the differential diagnosis, and certainly, when a frozen section is done on a cystic lesion of the ovaries from a pregnant patient, careful search for the distinctive features of follicle cysts and other changes of the intervening tissue that are seen in hyperreactio luteinalis, such as edema, should be sought. When a massive unilocular smooth-walled cyst is encountered in pregnancy, the large solitary follicle cyst should be considered. In contrast to most cystic granulosa cell tumors, it has a lining of cells with copious eosinophilic cytoplasm and, rather characteristically, focal bizarre nuclei. Possible early stages of the large solitary follicle cyst were identified in one study. Another cystic mass of pregnancy that is well known, a corpus luteum cyst (Fig. 61), was also considered in that report. This lesion of the first trimester was seen in 12 cases in that series, and ranged up to 10 cm. These smooth-lined cysts are similar to those seen outside the setting of pregnancy, and have the classic convoluted yellow rim.

The solid tumor-like lesion of pregnancy is the pregnancy luteoma, and it is well known that the diagnosis of steroid cell tumor should not be made in pregnancy unless a pregnancy luteoma has been ruled out. The pregnancy luteoma is often sizeable, with an average diameter of about 6 cm, but may range up to 20 cm, and may have a striking bosselated external surface, the overall features often quite reasonably suggesting the possibility of a neoplasm. They are bilateral in about one-third of the cases, and within an individual ovary, they are often seen in the form of multiple nodules, albeit they may become confluent when the lesions are large. The process is usually discovered at or near term, and the patients are typically asymptomatic, but about one-quarter of the cases are associated with androgenic manifestations appearing during the second half of pregnancy. Microscopic examination typically shows a more or less diffuse growth within the individual nodules, but it is often punctuated by follicle-like spaces containing eosinophilic colloid-like material (Fig. 62). The latter is a rare finding in the steroid cell tumor, the neoplasm most realistically in the differential diagnosis. The nodules are typically beefy red in contrast to the yellow appearance of many steroid cell tumors, although overlap exists. A well-known trap is the brisk mitotic activity of many pregnancy luteomas. The relatively common uterine lesion, placental site nodule, is rarely seen in the ovary, usually as a microscopic finding. The final tumor-like lesion is the incidentally discovered microscopic process known as granulosa cell tumorlets. They are unlikely to cause clinical mischief in as much as, even if erroneously considered, neoplasms, they would be tiny microscopic ones of no clinical consequence.

As the early reproductive era sees a peak in incidence of Sertoli–Leydig cell tumors and the majority of juvenile granulosa cell tumors and a sizable number of adult granulosa cell tumors occur in this age range, it is obvious that occasional patients with one of these neoplasms will be encountered while pregnant. A pitfall is that these neoplasms may show considerable intercellular edema, or be extensively luteinized, both features that may obscure their characteristic morphologic features and render them, on average, more difficult to diagnose than similar neoplasms encountered outside of the setting of pregnancy. Perhaps the most specific trap is that the edema may produce a pattern that simulates, at least to some degree, the reticular pattern of yolk sac tumor, and we have seen cases of sex cord-stromal tumors erroneously considered to be yolk sac tumors during pregnancy for this reason. Although thorough sampling is important at any time, it is particularly so when evaluating a perplexing mass lesion from a pregnant patient, because sometimes only minor areas will show diagnostic features of one or another form of sex cord-stromal tumor, making it evident that that is the diagnosis. As noted earlier, the enhanced luteinization of ovarian tumors during pregnancy may make weakly luteinized cells of the sclerosing stromal tumor more overtly luteinized and more copious in number, sometimes obscuring the nature of the underlying tumor.

Any ovarian neoplasm from a pregnant patient is more likely to undergo hemorrhagic infarction and rupture than outside the setting of pregnancy. This may result in a dramatic presentation, and the infarction often makes diagnostic foci limited and contributes to diagnostic difficulty. The topic of ovarian tumors in pregnancy has been periodically reviewed over the years, and for potential aid, selected references on the general topic are provided.

Another feature of ovarian tumors in pregnancy is their much greater tendency to exhibit stromal luteinization, which is often striking, and may be associated with dramatic androgenic manifestations. This is an example of the
phenomenon, named many years ago by Dr. Jack Morris and Dr. Scully as “ovarian tumors with functioning stroma” (Fig. 63).276 Dr. Scully maintained a great interest in this process, and endocrine aspects of the ovary and its tumors, over the years, and some of his original articles and reviews are worth consulting277–280 and accordingly cited for the potential aid of the reader, as is one of the best recent articles on the topic.281

The presence of androgenic manifestations due to a functioning stroma may result in a clinician thinking the patient has the most well-known androgenic neoplasm of young females, the Sertoli-Leydig cell tumor, and when encountering a tubular pattern in an ovarian tumor of a young virilized female, the pathologist quite reasonably wonders about Sertoli-Leydig cell tumor. However, in some cases of Krukenberg tumor, a striking tubular pattern simulates the Sertoliform pattern of a Sertoli-Leydig cell tumor, and the luteinization may be misconstrued as the Leydig cell component of a Sertoli-Leydig cell tumor.282 A number of the tubular Krukenberg tumors of the ovary described by us some years ago were misdiagnosed as Sertoli-Leydig cell tumors for the reasons just summarized. Although essentially any ovarian tumor may be luteinized during pregnancy, particular mention should be made of its occurrence in mucinous cystic tumors, simply because they are the most likely surface epithelial neoplasms to be found in pregnancy. Additionally, dysgerminoma and yolk sac tumor each may show striking stromal luteinization, although in a dysgerminoma in particular, it also sometimes is due to syncytiotrophoblast giant cells. Enigmatically, teratomas are less often luteinized than other neoplasms that are likely to be seen in a pregnant patient.

For obvious reasons, cases of gestational trophoblastic disease occur in relatively young patients, and many of them are in the early reproductive era within the span of years of interest here. The majority of reported cases have been choriocarcinomas, but sporadic examples of hydatidiform mole have been described,283 as have been even rare cases of placental site trophoblastic tumor284 or epithelioid trophoblastic tumor.285 As is typical, choriocarcinoma usually forms a large, solid, hemorrhagic mass that may be associated with rupture and hemoperitoneum and significant symptomatology. Cases of molar disease may also be hemorrhagic but less diffusely so, with vesicles often being noted. There are no distinctive gross features of the other rarer forms of trophoblastic disease seen in the ovary. The microscopic aspects of these processes are as seen in the uterus.

Other pregnancy-related lesions that may be seen due to pregnancy include even an ectopic pregnancy itself,286 which may form a hemorrhagic mass (Fig. 64), and ectopic decidua, the latter not likely to form a sizeable mass but potentially problematic on microscopic examination in as much as rarely decidual cells may have a somewhat signet ring-like morphology. A decidual reaction is present in essentially all
ovaries at term and may be seen as early as 9 weeks of gestation. Rarely, ectopic decidua is particularly significant to the patient, as it has been associated sporadically, usually when having a more extensive peritoneal distribution, with massive, sometimes fatal, intra-abdominal hemorrhage. This complication may also be seen in rare cases as a result of the marked decidual change of the endometriotic stroma of endometriosis of a pregnant patient, leading to softening of the cyst wall and perforation of it. Another pitfall associated with endometriosis rarely is a Arias-Stella-type change in its epithelial cells, potentially resulting in an erroneous diagnosis of carcinoma. On histologic examination, decidual cells in non-endometriosis-associated lesions typically occur in the superficial cortical stroma, or in the surface including within adhesions. The error of misinterpreting decidual cells with signet ring change as true neoplastic signet ring cells can be avoided if one observes a spectrum from the signet ring-like cells to more typical decidual cells, but awareness of this phenomenon can be crucial. Sometimes decidual cells exhibit limited nuclear atypia and hyperchromasia, which can also lead to a misinterpretation. Occasionally, foci of decidua show smooth muscle metaplasia, and this can rarely be associated with the phenomenon of leiomyomatosis peritonealis disseminata. In contrast to non-endometriosis-associated decidual change, that association with endometriosis typically is seen within the parenchyma, although it can be seen on the surface. Finally, hilus cell hyperplasia may be seen in response to pregnancy, and the mere presence of an ovarian mass may on a simple mechanical basis cause difficulties in delivery.

Tumor-like lesions (non-pregnancy related)

This is the final but important category of mass lesions of the ovary in general, and because of space limitations, here I will only discuss those that typically occur in the young or comment on any special aspects of these lesions relevant to them when seen in the young. Coverage of endometriosis, arguably the commonest disorder in this entire category, concludes the article, even though some feel that endometriosis should be considered in the neoplastic family. We have followed the traditional approach of considering it non-neoplastic here, although it is well known that it can undergo malignant transformation.

The commonest group of lesions in this category are the familiar cysts of follicular derivation, both follicle cysts and corpus luteum cysts. They have three main complications (other than prompting the need for an operation to exclude a neoplasm): sexual precocity due to follicle cysts; torsion, particularly common in the case of neonatal follicle cysts, and hemoperitoneum, rarely even resulting in death.

Follicle cysts have three peaks, in the neonatal period (Fig. 65), around the menarche, and in the perimenopausal years, but are not rare at any time in the reproductive years. Any series of mass lesions in the ovary from a children’s hospital will have a significant contribution provided by neonatal follicle cysts that arise because of in-utero stimulation by maternal hormones. Although these develop in-utero, they may remain for some time and become symptomatic after the neonatal period is over, such as the example we illustrate in a 9-month-old girl. Neonatal follicle cysts may be large, average size 8.3 cm as noted earlier, the largest documented size we encountered in preparing this review being 13 cm. Occasionally, there is ascites or maternal polyhydramnios. After the first year, follicle cysts become rare until puberty, although small cysts not large enough to be follicle cysts are common on ultrasonography. In older girls, follicle cysts may

Fig. 63 – Yolk sac tumor with prominent stromal luteinization. This is an example of the phenomenon of so-called “ovarian tumor with functioning stroma.”

Fig. 64 – Ectopic ovarian pregnancy. This hemorrhagic mass ruptured and resulted in exsanguination of the teenage patient.
cause isosexual pseudoprecocity. Follicle cysts in general are frequently encountered in the reproductive years and are generally small, but definitively over 3 cm (to distinguish them from cystic follicles), lesions with a thin, smooth cyst wall. In the Boston Children’s experience, those in postmenarchal girls had an average diameter of 4.7 cm. Larger examples in particular may be impossible to distinguish grossly from neoplastic cysts, such as cystic granulosa cell tumors, although their walls are typically thinner, and this should not be an issue on microscopic examination although denudation of the lining cells of follicle cysts sometimes may result in a need for additional sampling. The typical lining of small granulosa cells with uniform nuclei and typically, but not always, appreciable eosinophilic cytoplasm is characteristic (Fig. 66). Corpus luteum cysts have only rarely been described in neonates and for practical purposes are cystic lesions of the reproductive era. Their cerebriform golden-yellow periphery helps distinguish them grossly from follicle cysts, but their smooth lining is similar. On microscopic examination, they generally have a thicker lining of larger cells with more conspicuous cytoplasm and a convoluted pattern with wedge shape invaginations containing blood vessels. Corpus luteum cysts may be associated with menstrual irregularities and rarely either form of cyst may rupture with hemoperitoneum, which has been fatal on occasion. It is worth briefly noting that even torsion with hemorrhagic infarction of a non-neoplastic ovary may cause confusion with a neoplasm, and thorough sampling may be needed to exclude neoplasia.

Polycystic ovarian syndrome (Stein–Leventhal syndrome) is a time-honored non-neoplastic abnormality of the ovary, but examples are very rarely encountered by the pathologist nowadays because of the sophisticated hormone evaluation and medical management of these cases. However, it is pertinent to note this disorder as it typically occurs in young patients. Disorders in the stromal hyperplasia–stromal hyperthecosis category are seen on average at an older age than cases of polycystic ovarian disease, but they may be seen in the young, and striking examples may result in modest ovarian enlargement that is typically bilateral. Stromal hyperthecosis may be associated with androgenic or estrogenic manifestations and occasional cases are associated with insulin resistance, sometimes accompanied by diabetes, acanthosis nigricans, and hyperandrogenism (the so-called hair-an syndrome). Ectopic decidua has been mentioned in the section on pregnancy-related lesions, but may be seen in nonpregnant patients, sometimes in response to the presence of a functioning ovarian tumor or after radiation therapy. In this setting, as in pregnancy, it is usually an incidental microscopic finding, but rarely small hemorrhagic nodules may be visible on the ovarian surface.

Fig. 65 – Follicle cyst in 9-month-old girl. This cyst was initially demonstrated in-utero, and by the time it was removed it had undergone extensive infarction.

Fig. 66 – Follicle cyst. Typical low-power appearance (A). Many layers of cells are present, and the cytoplasm is not as abundant and eosinophilic, at least in upper layers, as is often the case (B).
Two processes with a very definite tendency to occur in the young are massive edema and fibromatosis. Nine of the 11 cases of massive edema we reported were from patients under 30 years of age. The youngest was a 9-year-old. A similar tendency for fibromatosis to occur in the young was also exhibited by our experience, 10 of 11 patients with generalized fibromatosis being in the first three decades. The youngest in that group was a 13-year-old. Both these conditions are rare, fibromatosis particularly so. The clinical presentation is variable, including in some cases evidence of androgen excess due to stromal luteinization and in others, particularly massive edema, significant abdominal pain due to frequent torsion. Though usually unilateral, bilateral cases are encountered. Microscopically, each process is similar in as much as one sees either edematous or fibromatous tissue coursing between residual follicular derivatives, and this may be appreciated grossly because of the presence of scattered small cysts on the background of a watery sectioned surface in the case of massive edema or a firm sectioned surface in the case of fibromatosis. The incorporation rather than effacement of preexistent ovarian structures is an important distinguishing feature between these non-neoplastic entities and conventional or edematous fibromas. The only other microscopic finding of note is the occasional presence of lutein cells, which explains hormone excess, if present.

The important non-neoplastic peritoneal lesion, peritoneal inclusion cyst, is not rare in the young, as many as 40% of the patients in a series being in the first three decades. Ovarian involvement is not rare, but it is usually clearly seen to be a surface process and not generally confused with an ovarian neoplasm, but parenchymal involvement may be seen, and in the setting of widespread adhesions and distortion of the anatomy, the clinical presentation may be that of an ovarian mass. Recognition of this lesion should be straightforward.

Fig. 67 – Endometriotic cyst with lining of pus in a young patient who had life-threatening infection.

Fig. 68 – Endometriotic cyst with infection (A). The endometriotic nature of the lining of the cyst is evident on high power, and pus can be seen in the lumen (B).
Concluding remarks

In this article, some of the important and often intriguing clinical aspects of ovarian masses in young females have been highlighted and the gross and microscopic features of these diverse lesions as well as their differential diagnosis have been elaborated. Many of them are amongst the most interesting in the entire spectrum of ovarian pathology. The lesions range from relatively common to distinctively rare, but all are important for pathologists to be aware of because of the often crucial therapeutic and prognostic significance of correct interpretation in young individuals in whom conservative management with preservation of reproductive function is almost always a goal.

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Gonadoblastoma and selected other aspects of gonadal pathology in young patients with disorders of sex development

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\textbf{A B S T R A C T}

Some patients with disorders of sex development (DSDs), previously known as intersex disorders, have abnormal gonadal development and an increased risk of germ cell tumors. Because of their relative rarity, however, many pathologists are unfamiliar with the morphological findings in the gonads of DSD patients and their clinical significance. This review concentrates on some of the most common DSDs where gonadal specimens may come to the attention of pathologists. It highlights the findings in gonadal dysgenesis, a DSD with a spectrum of clinical, pathologic, and molecular features but with the shared attributes of having both Y chromosomal material (even if in very limited amounts) in the gonad and also having mutations or deletions in genes necessary for normal gonadal development, mostly in those upstream of the \textit{SOX9} gene. This situation results in testicular tissue lacking normal Sertoli cells, which are now considered an essential element for the normal maturation of the primordial germ cells that migrate to the gonad from the embryonic yolk sac. Germ cells with delayed maturation mimic neoplastic germ cells, but there are both morphological and immunohistochemical differences. If the gonad having germ cells with delayed maturation also harbors the \textit{TSPY} gene on the GBY locus of the Y chromosome, the cells may undergo neoplastic transformation and result in the distinctive gonadoblastoma, whose pathologic features are explored at length herein, including its potential for variant morphologies, such as a “dissecting” pattern. Another important DSD, the androgen insensitivity syndrome (AIS), is discussed at length, including the varied appearances of the testis and its distinctive lesions—hamartomas and Sertoli cell adenomas. The potential for germ cell neoplasia in the partial AIS is also discussed and contrasted with that of the complete AIS. A third major topic is ovotesticular DSD (true hermaphroditism). The clinical features and morphology of this condition are reviewed, including the arrangements of the tissue components in an ovotestis. Several other DSDs with distinctive gonadal findings are also considered, including Klinefelter syndrome, 5\textalpha-reductase deficiency, 17\beta-hydroxysteroid dehydrogenase deficiency, and female adrenogenital syndrome.

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Introduction

Patients with disorders of sex development (DSDs), previously known as intersex disorders but changed at the recommendation of an international consensus conference of experts in the field, may develop gonadal lesions and neoplasms that come to the attention of pathologists. These have varied histopathologic features that few have significant experience with and can easily cause problems in interpretation. The patients are often young (in the first 3 decades of life) and, accordingly, merit consideration in this focused review of gonadal tumors and tumor-like lesions in the young. DSDs are also complex clinically and have varied underlying pathogeneses that include karyotypically detectable chromosomal anomalies, mutations involving pathways essential for normal gonadal development, genetic changes that affect the biosynthetic pathways or mechanisms of action of sex hormones, and exposure to exogenous agents. This article does not represent a comprehensive review of this topic. Instead, it concentrates on those conditions having distinct gonadal findings that pathologists may encounter (even if infrequently) and that typically present in patients younger than 20 years. The reader requiring a more thorough exploration of the clinical features, including the nongonadal findings, and the underlying genetic or metabolic mechanisms in pathologic details continue to evolve.

Gonadal dysgenesis and gonadoblastoma

Gonadal dysgenesis represents improper development of the gonad with frequent loss of the normal compartmental organization as well as abnormalities in the sex cord and germ cell components. A shared finding in patients with gonadal dysgenesis is a mutation in at least one of the many genes involved in the normal development of the gonad. These include the WT1 gene, resulting in the formation of a dysgenetic testis in 46,XY individuals who, depending on the particular mutation, develop the Denys–Drash, Frasier, or Wilms tumor, aniridia, genitourinary anomalies, and retardation (WAGR) syndromes. Similarly, mutations in SRY, SOX9, DHX, ARX, NR5A1 (SF1), and TSPYL1 have resulted in dysgenetic testes in 46,XY patients. Female or ambiguous external genitalia are common to all of these conditions. Gonadal dysgenesis that retains more than a rudimentary resemblance to an ovary, in contrast to testicular dysgenesis, is rare. Ovarian maldevelopment occurs most commonly in 45,XO patients with Turner syndrome, who develop “streak” gonads consisting of gonadal stroma with greatly reduced or absent germ cells and sex cord cells. Similar streak gonads have also been found in 46,XX phenotypic females in the second decade with leukodystrophy. Autosomal trisomies may also result in streak morphology manifest in infancy. Patients with 46,XX DSDs who have mutations in SRY, RSPO1, and WNT4 may develop an ovotestis, a condition sometimes referred to as “true hermaphroditism,” and, although abnormal, such gonads are not classified as part of gonadal dysgenesis.

Mixed gonadal dysgenesis usually develops in patients with either a 46,XY or 46,XY/45,XO mosaic karyotype. As originally defined, it is referred to the presence of an abnormal “dysgenetic” testis on one side, with the opposite side having no gonad or a streak/rudimentary gonad. It has become clear, however, that patients with bilateral dysgenetic testes and many Y chromosome-positive patients with bilateral streak gonads (definitional, “pure” or “complete” gonadal dysgenesis) have features identical to those with mixed gonadal dysgenesis. Most patients have ambiguous external genitalia, which cause them to come to medical attention in the neonatal period, and most (70%) are reared as females. Patients with 46,XY/45,XO mosaicism may have stigmata of Turner syndrome. Amenorrhea may be a presenting feature in teenagers.

The dysgenetic testis may be intraabdominal, in the inguinal canal, or scrotal. It is smaller than normal and, because of abnormal thinning of the tunica albuginea, its external aspect may be brown or pink rather than the normal white appearance (Fig. 1). Occasionally it may show pink–yellow spots on its surface due to penetration by underlying seminiferous cords. It may be attached to the epididymis by only a thin fragment of connective tissue. About 40% have an associated fallopian tube. On microscopic examination, the testis has a thin tunica albuginea with a stroma that may resemble that of the ovarian cortex. Immediately subjacent, solid seminiferous tubules (or seminiferous cords) form an anastomosing network in a widened, edematous interstitium and penetrate the inner aspect of the tunica albuginea. More deeply, the tubules have a normal, closely packed, and non-

![Fig. 1 – A 0.8-cm, bivalved dysgenetic testis showing a pink-tan external surface (lower) and tan cut surface.](Image 306x67 to 541x318)
branching arrangement (Fig. 2). The tubules/cords consist of immature Sertoli cells and a variable number of germ cells, with the former usually predominating. Leydig cells with scant amounts of amphophilic cytoplasm are seen in small clusters in the interstitium. The germ cells of seminiferous cords may resemble embryonic germ cells (gonocytes) or spermatogonia. Often they diminish in number or disappear as the patient ages through a process of apoptosis (Fig. 3). Some may persist in an immature state, and it is currently felt that these are the cells that are susceptible to malignant transformation, thus becoming intratubular germ cell neoplasia, unclassified type (IGCNU). Germ cells with “delayed maturation” in the seminiferous tubules of dysgenetic testes retain positivity for the immunohistochemical markers that are commonly used to aid in the recognition of IGCNU [i.e., placental alkaline phosphatase (PLAP), OCT4, CD117, NANOG, and others] and it is important not to overdiagnose them as IGCNU. Germ cells with delayed maturation are often positioned in the central or suprabasilar portion of the seminiferous tubules (Fig. 4) whereas IGCNU is consistently at the base. Additionally, it has been shown that in contrast to IGCNU, germ cells with delayed maturation do not express stem cell factor (SCF), also known as c-kit ligand.

The pathogenesis of streak gonads, specifically their “intended” development, is not clear. There is some evidence that at least some streaks are malformed ovaries by virtue of the identification of rare “primordial follicles” within them, but it is arguable whether such a structure is sufficient to recognize a gonad as an ovary. They grossly appear as firm, white-gray, ovoid to elongated structures that are rarely larger than 1 cm (Fig. 5) and almost always associated with a fallopian tube and usually an infantile uterus. On microscopic examination, streaks, in their earliest phase, consist of a disorganized admixture of germ cells with closely associated sex cord cells in poorly defined nests and cords (Fig. 6).
Many of the germ cells have a primitive, gonocyte-like appearance. In studies of gonadoblastomas, similar-appearing tissue is commonly found associated with the tumor and has been termed “undifferentiated gonadal tissue,” although this also has a component of neoplastic germ cells, which is not necessarily the case with early gonadal streaks. With time, however, both the germ cell and sex cord components of gonadal streaks regress, although occasional remnants of the latter persist, and the gonad consists almost exclusively of dense nonspecific gonadal stroma (Fig. 7). In one study, these changes occurred between 1 week and 1 year of age as shown in separate tissue samples. Pertinent to the ensuing discussion concerning gonadoblastoma, it seems quite likely that persistence of the initially present germ cell and sex cord components, with the former’s content of cells with delayed maturation, is responsible for the generation of gonadoblastoma associated with streak gonads (about 20% of cases).

Gonadoblastoma is a neoplasm that was first documented in 1953 by Dr. Robert Scully; he initially identified the index case during his preparation to present a case of “dyserminoma” at one of the famed exercises, “Case Records of the Massachusetts General Hospital.” He defined the tumor based on its strong resemblance to the embryonic gonad while in an “indifferent” state of development. He subsequently uncovered an old case that had also been the subject of a similar presentation in 1937. These two cases were the basis for the 1953 report. Seventeen years later, he published the definitive study of gonadoblastoma involving 101 cases in 74 patients.

Gonadoblastoma occurs in young patients with gonadal dysgenesis. In the single largest series, the ages at presentation ranged from 1 to 38 years, with the majority presenting prior to 15 years. More recently, a gonadoblastoma was found in the testis of a 46,XY fetus of 28-week gestational age. The patients frequently have phenotypic anomalies of sex development, consistent with a DSD. The greatest number of patients (approximately 45%) appear as virilized females, with about 20% having a male phenotype but with hypospadias and ectopic testes; the remainder are nonvirilized females. Karyotypes are mostly 46,XY or 46,XY/45,XO. Cases reported in 45,XO patients with a Turner phenotype are felt to represent nondetected mosaicism with the peripheral karyotype believed not to represent cells containing at least a portion of the Y chromosome within the dysgenetic gonads. The testis-specific protein Y encoded (TSPY) gene near the centromere of the Y chromosome, in a region designated the GBY locus, is now considered an essential element for the formation of gonadoblastoma.

Currently, most patients with gonadoblastoma are identified in infancy or early childhood as they are investigated for ambiguous external genitalia. Because some patients may not have clear external abnormalities, they may present later, chiefly during the investigation of primary amenorrhea among the phenotypic females. This was the major mode of discovery in the past during an era that was not as sensitized to the possibility of germ cell neoplasia in this context.

The gonad that harbors a gonadoblastoma can be identified as either a testis or a streak in about 20% of cases each. In the remaining majority, however, its nature is not clear because of replacement by either gonadoblastoma or an invasive germ cell tumor (see below). In phenotypic females, bilateral fallopian tubes are almost invariably present but only one fallopian tube is usually present in the phenotypic males. Regardless of gender phenotype, an infantile uterus is seen. Male internal genitalia (epididymis, vas deferens, and prostate) are more commonly found in phenotypic males than in phenotypic females. About 40% of gonadoblastomas occur bilaterally.

On gross examination, the gonadoblastoma is tan-yellow to gray, firm, and often has a granular appearance and gritty quality on sectioning that reflects its frequent conspicuous calcifications (Fig. 8). It may be juxtaposed to an invasive germ cell tumor, usually a germinoma that shows the characteristic solid, fleshy, cream-colored to tan, lobulated appearance. On microscopic examination, the classical appearance is that of multiple, discrete, round, and relatively small nests that are dispersed in a nonspecific, spindle cell gonadal stroma that contains occasional Leydig-like or lutein-like cells lacking Reinke crystals (Fig. 9). The nests
comprise germ cells, small sex cord cells, and round deposits of eosinophilic basement membrane material (Fig. 10). This material appears to act as a nidus for calcifications that initially may appear psammomatous but frequently coalesce into larger aggregates, sometimes developing a mulberry-like shape (Fig. 11). Occasionally, the cellular components of a gonadoblastoma regress, leaving as remnants the characteristically shaped calcifications (Fig. 12), a feature considered diagnostic of a “burnt-out” gonadoblastoma. The sex cord cells have angulated nuclei and inconspicuous cytoplasm and may be arranged at the periphery of the nests in a palisaded fashion (coronal pattern), around the basement membrane deposits (Call-Exner-like pattern) or encircling individual germ cells (follicle-like pattern). The germ cells vary in appearance, with the relative proportion of different forms also being variable from nest to nest and from case to case (Fig. 10). At least some of the germ cells in gonadoblastomas resemble those of IGCNU or seminoma/dysgerminoma; these have the characteristic pale to clear cytoplasm and polygonal, “squared-off” nuclei with one or more prominent nucleoli. Others, however, have a spermatogonium-like appearance with less conspicuous cytoplasm, finely granular to ropy chromatin, and small to inconspicuous nucleoli. This heterogeneity is also reflected in Feulgen-based microspectrophotometric DNA measurements, which document separate aneuploid and diploid cell populations, as well as immunostaining for neoplastic germ cell markers (Fig. 13).

A recent observation documents the presence of a distinctive, likely precursor to gonadoblastoma in 33% of dysgenetic gonads. If the dysgenetic gonad harbored a gonadoblastoma, this precursor, termed “undifferentiated gonadal tissue,” was found in at least 50% of the cases, with those lacking it often having no residual noninvolved tissue. Undifferentiated gonadal tissue consists of germ cells with sex cord cells, either in small loose clusters or poorly defined cords, or in isolation in a background of gonadal stroma (Fig. 14). The clustered and corded pattern was recognized by Dr. Scully as
“dissecting gonadoblastoma,” and the accuracy of this interpretation is supported by the identical immunohistochemical staining properties of the germ cells in undifferentiated gonadal tissue and gonadoblastoma for a number of neoplastic and nonneoplastic markers, including OCT4, PLAP, CD117, TSPY, and VASA.24 Classic gonadoblastoma, it appears, may represent a progression of undifferentiated gonadal tissue with the formation of larger, cohesive nests of the germ cell and sex cord components. On occasion, we have seen examples of dissecting gonadoblastoma that consist of large anastomosing nests with inconspicuous basement membrane deposits that closely resembled invasive germinoma at low-power examination (Fig. 15) until the sex cord cells within the lesion were appreciated at higher magnification. An important practical implication concerning undifferentiated gonadal tissue, given its precursor role for gonadoblastoma and its component of neoplastic germ cells, is that it carries the same treatment implications for gonadectomy as gonadoblastoma itself. This point is particularly relevant when it is identified in a biopsy of a patient being investigated for possible gonadal dysgenesis.

If gonadoblastomas are left in place, a high proportion of them progress to an invasive germ cell tumor. In the original series of Scully, 57% of patients also had a germinoma, 4% either embryonal carcinoma or yolk sac tumor, and 4% teratoma.29 Given their analogy with testicular IGCNU, it is likely that all would eventually progress to invasive tumors. Because such progression may be seen in children in the first decade, gonadectomy should be performed as soon as either undifferentiated gonadal tissue or gonadoblastoma is identified.

The germinomas that complicate many gonadoblastomas show the characteristic features of that neoplasm. Most commonly, the tumor forms either sheets that are interrupted by thin, fibrovascular septa bearing a lymphoplasmacytic infiltrate or it is arranged in smaller, anastomosing nests that are separated by a fibrous stroma. Trabecular and corded patterns may also be seen. The cells are characteristically round with polygonal nuclei with linear edges and one or two prominent nucleoli. The cytoplasm is often pale to clear with distinct membranes. Clusters of epithelioid histiocytes occur in up to half the cases and scattered syncytiohytrophoblast cells in a minority. If the germinoma developed in a dysgenetic testis, some of the tubules may become distended with neoplastic cells, a finding sometimes termed “germinoma in situ.” If a germinoma contains prominent clusters of calcification, and especially if these have the distinctive “mulberry-like” configuration, the possibility of an overgrown gonadoblastoma and underlying gonadal dysgenesis merits strong consideration. This is clinically important because of the high risk of bilateral tumors in that circumstance.29 It is prognostically and potentially therapeutically important to distinguish invasive germinomas from those “dissecting” gonadoblastomas that mimic them. This is based on the consistent presence of a sex cord cell component in the dissecting gonadoblastomas, a finding that

Fig. 12 – A “burnt-out” gonadoblastoma showing the characteristic mulberry-shaped calcifications in a streak gonad.

Fig. 13 – The germ cells are variably reactive for OCT4, a sensitive neoplastic germ cell marker, in this nest of gonadoblastoma.

Fig. 14 – Undifferentiated gonadal tissue, a lesion sometimes termed “dissecting gonadoblastoma,” surrounds two nests of gonadoblastoma.
often focally distributed in the Sertoli cell nodules, the surrounding parenchyma does not contain nonspecific (ovarian-type) gonadal stroma, and the sex cord cells are fetal-type Sertoli cells that are strongly and diffusely reactive for SOX9 and negative for FOXL2. Furthermore, the patients are normal, phenotypic, postpubertal males who do not have a DSD. The incompletely differentiated sex cord cells in gonadoblastomas and the dysgenetic gonads that contain them appear to play an important role in the development of gonadoblastoma. Despite the fact that the dysgenetic gonads consistently contain Y chromosomal material with the GBY locus/TSPY gene, properly formed Sertoli cells, as reflected by strong and diffuse SOX9 reactivity, are absent. Several genetic syndromes with a predisposition to forming gonadoblastomas are known to carry mutations in genes that are upstream to SOX9 and are required for the normal expression of SOX9. These include Frasier and Denys–Drash syndromes, both of which are associated with different mutations in WT1, and also Swyer syndrome (46,XY pure gonadal dysgenesis), which has several implicated mutations, most commonly SRY but also DHH, NRSAI, and WNT4, as well as 3p deletion. Functional Sertoli cells are required for the normal maturation of the primordial germ cells/gonocytes that migrate from the yolk sac to the developing gonad. Many of these cells, it is believed, therefore fail to mature but remain in an immature, gonocyte-like state with the continued expression of fetal/neoplastic germ cell markers in the postnatal period. These germ cells are then susceptible to malignant transformation under the action of TSPY, which promotes cellular proliferation.

**Androgen insensitivity syndrome**

Patients with the androgen insensitivity syndrome (AIS) are genotypic males with a 46,XY karyotype who have mutations in the X-linked androgen receptor that causes the receptor-bearing target cell to be either unresponsive or incompletely responsive to androgen. The resultant conditions are known as complete and partial (or incomplete) AIS (CAIS and PAIS), respectively. CAIS is approximately 10-fold more common than PAIS. These are conditions that commonly present in young patients with the clinical picture differing depending on the complete or partial nature of the AIS.

The initial complete characterization of CAIS is generally attributed to Morris, a gynecologist, who reviewed the clinical features of 82 patients in 1953, with earlier reports limited to individual cases or small series. It should be noted that the pathologic findings in that study were provided by Dr. Robert Scully but were not so acknowledged. It is from this study that the well-known phenotype of CAIS patients, namely young women with fully developed female secondary sex characteristics and body habitus but with absent or scanty pubic and axillary hair, became established. The term used by Morris, “testicular feminization,” has been replaced by AIS. These patients have high levels of circulating testosterone and luteinizing hormone, and their female secondary sexual features are explained by aromatase conversion of androgens to estrogens.

The description of PAIS is usually attributed to Reifenstein, who described a kindred with “hereditary familial
hypogonadism” in an abstract in 1947. Bowen et al.\textsuperscript{45} popularized the eponym “Reifenstein syndrome” in their more definitive characterization in 1965. At that time, they speculated that a possible cause was either a “deficiency in the secretion of the Leydig cells or insensitivity of the end organ structures,” although they, incorrectly, favored the former. PAIS, as described by Bowen, was characterized by hypospadias, gynecomastia, female habitus, light or absent beard, and postpubertal testicular atrophy.

CAIS

The prevalence is estimated to be one in 20,000–99,000 genetic males.\textsuperscript{7} Patients generally present as phenotypic females either in infancy, when ectopic testes manifest as labial swellings or within bilateral inguinal hernias, or in adolescence because of primary amenorrhea. In the series of Rutgers and Scully,\textsuperscript{42} 35% of the CAIS patients had a history of prepubertal inguinal herniorrhaphy, and 43% presented with primary amenorrhea. It is estimated that about 1% of prepubertal girls with inguinal hernias have CAIS.\textsuperscript{46,47} More recently, patients are discovered in early childhood after genetic testing that is prompted by a family history or by a disparity of phenotypic sex at delivery and antenatal-determined karyotype from amniocentesis.\textsuperscript{7} Presentation in later adolescence may, uncommonly, be due to detection of a pelvic mass that reflects a germ cell tumor.

The mutations responsible for AIS are missense mutations leading to amino acid substitutions predominantly in the ligand-binding or DNA-binding domains of the coded protein. Over 800 such mutations have been identified,\textsuperscript{7} which are detectable using currently available DNA sequencing technology.

The testes are ectopic, with abdominal location (78%) predominating over inguinal (22%).\textsuperscript{52} On gross examination, they usually contain multiple tan to white nodules that vary from microscopic to over 10 cm but that typically are about 2 cm (Fig. 16). An irregularly shaped smooth muscle mass with a white whorled cut surface, usually about 2 cm, is attached to the medial aspect of the testis (Fig. 16) and felt to represent a uterine anlage but without any endometrial cavity. Paratesticular cysts may be present, sometimes measuring several centimeters in diameter (Fig. 16).\textsuperscript{43} About one-third of patients have at least one adjacent fallopian tube, but these are often not grossly appreciated.

Apart from the distinct nodules, Rutgers and Scully\textsuperscript{72} described four patterns of parenchymal organization: diffuse tubulostromal (Fig. 17), lobular tubulostromal, mixed diffuse and lobular tubulostromal, and stromal predominant (Fig. 18). As the designations imply, the first three are characterized by diffuse and/or lobular arrangements of densely packed, spindled stromal cells with seminiferous tubules and variably prominent Leydig cells, with those cases with a lobular component having an intervening loose, fibrous stroma. The tubules are mostly small and solid and lined by immature Sertoli cells (Fig. 18). The germ cell component varies by
age; in infants and toddlers, the number of spermatogonia may be normal, but there is a rapid loss after a few years of age so that only a minority retain recognizable germ cells in later childhood and adolescence.42,48 The stromal-predominant pattern shows an organization of stroma resembling that of the ovary with sparse, small seminiferous tubules, and Leydig cells. The Leydig cells in all patterns only rarely contain recognizable crystals of Reinke.

The majority of the nodules are hamartomas (Fig. 19), which are found in over 60% of the cases,42 with most of the remainder being Sertoli cell adenomas, present in about 20%. The hamartomas consist of small tubules lined by immature Sertoli cells with abundant numbers of intervening Leydig cells and only occasional spindle cells and smooth muscle cells. Occasional spermatogonia may be seen in focal tubules. The adenomas (Fig. 20) consist of nodules of tubules lined by fetal-type, immature Sertoli cells; in some cases, there are foci with conspicuously thickened surrounding basement membranes (Fig. 20). They differ from the hamartomas by their lack or paucity of Leydig cells.

An infrequent finding in CAIS patients is a tumor resembling the sex cord tumor with annular tubules (SCTAT), a neoplasm characteristically found as small nodules in the ovaries of young patients with the Peutz-Jeghers syndrome49,50 (see article in this issue on ovarian pathology in young patients). At least four such cases have been described in patients 18–20 years old and measured up to 8 cm;42,51,52 they had solid and cystic areas and showed the characteristic arrangement of sex cord cells with pale cytoplasm and antipodally placed nuclei around globular deposits of eosinophilic basement membrane. Malignant behavior of CAIS-associated SCTATs has thus far not been reported. Additionally, groups of small “dysgenetic” tubules, sometimes anastomosing, and occasional tubules containing large Sertoli cells with coarse, eosinophilic cytoplasmic granules (Fig. 21) are found in a minority of patients older than 12 years.42,53 Nodular aggregates of Leydig cells occur in about 25% of the cases. In contrast to Y chromosome-bearing gonadal

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**Fig. 19** – A hamartoma in CAIS consisting of a circumscribed nodule of uniform, solid, immature tubules lacking germ cells and with intervening Leydig cells (A), better appreciated at higher magnification (B).

**Fig. 20** – A portion of an adenoma in CAIS shows a circumscribed nodule with closely packed immature tubules and focally thickened basement membranes. Leydig cells are not apparent.

**Fig. 21** – Enlarged tubules with granular, eosinophilic cytoplasm in AIS.
dysgenesis, classic gonadoblastoma is a rare finding in CAIS, although at least one case with a well-characterized AR mutation has been reported.54

One of the most important questions concerning the gonads of CAIS patients is the risk for malignant tumors. In contrast to the situation with Y chromosome-bearing gonadal dysgenesis, where such risk has been estimated to be as much as 35%, with some variants (Denys–Drash and Frasier syndromes) being even more,55 CAIS has a low risk of germ cell neoplasia, estimated recently as low as 0.8%,55 although Manuel et al.56 in 1976, placed it at 3.6% by age 25 years. Additionally, when IGCNU develops in CAIS, it occurs in postpubertal patients.42,53 Among 40 patients with CAIS, the only patient younger than 20 years who developed a germ cell tumor was a 17-year old who had IGCNU with focal intertubular invasion.42 Similarly, among 44 CAIS patients, Hannema et al.53 found two cases of IGCNU, only one of which was in a patient younger than 20 years (a 17-year old). Others, however, have infrequently found invasive germinomas in adolescent girls with CAIS.57 Cools and Looijenga estimated the risk of IGCNU overall to be 5% and mostly in adult patients.58 As a consequence of these considerations, it is considered justifiable to delay gonadectomy in CAIS patients into late adolescence after full female secondary sex characteristics have developed. Follow-up by physical examination and imaging is important. One must be aware, however, that there are always exceptions to these general guidelines as, for instance, a rare report of an invasive yolk sac tumor that occurred in a 17-month-old patient.59

A potential diagnostic problem is the distinction of IGCNU in CAIS patients from germ cells with delayed maturation, which may have a primordial germ cell-like morphology that mimics IGCNU and that, like IGCNU, express fetal germ cell markers such as PLAP, OCT3/4, and AP2γ.20,23 Such cells, however, do not show a predominant basal position in the seminiferous tubules, unlike IGCNU, and it has been proposed that they can be distinguished from IGCNU by their negativity for SCF.23

PAIS

Patients with PAIS are 46,XY males with a variety of missense mutations in the androgen receptor that impairs its function to variable degrees. Most present in the neonatal period because of ambiguous external genitalia and hypospadias.7 The testes are ectopic, usually inguinal or abdominal, and may have a midline smooth muscle structure suggesting a rudimentary uterus.42 In a study of three cases, the diffuse tubulostromal pattern was exclusively found, with the tubules either being small and solid or larger with lumens.42 They are lined by Sertoli cells that are typically of the small, immature type but that may also be larger and sometimes have coarsely granular eosinophilic cytoplasm.42 Germ cells are typically sparse to absent and Leydig cells prominent. Maturation beyond spermatogonia is usually absent but may occasionally be found to spermatoctyes or spermatids.20 Fallopian tubes are identifiable in the paratestis in some cases. When germ cells persist, they may appear cytologically atypical and express the fetal germ cell markers that also are seen in IGCNU. Current thinking is that this finding may represent maturation delay rather than IGCNU, but these can be distinguished by the central position of germ cells with maturation delay and their nonsegmental distribution in the testis.20 IGCNU, on the other hand, is segmental and basilar. The fate of maturation delayed germ cells is likely variable, with some eventually progressing to IGCNU (Fig. 22) and with others undergoing apoptosis or maturing to spermatogonia. The risk of germ cell neoplasia in PAIS is higher than in CAIS and has been estimated at 15%.60 It seems likely that studies showing a very high frequency of IGCNU in PAIS (73% in one report of 11 cases61) may have interpreted some cases that now would be considered as maturation delay as IGCNU. Verified IGCNU, however, may be seen in PAIS patients as young as 13 years of age.20

Ovotesticular disorders of sex development

Patients with an ovotesticular DSD (previously termed “true hermaphroditism”) by definition have both ovarian and testicular gonadal tissue. Various combinations are possible, including bilateral ovotestis (30%), testis opposite ovary (20%), ovary with ovotestis, and testis with ovotestis.54 The patients’ karyotypes may be 46,XX (usually); 46,XY (least commonly); or mosaic. It is an uncommon condition, with only approximately 500 cases reported worldwide.7 Ovarian-bearing tissue is more common on the left side and testicular on the right. The patients often present in infancy with ambiguous genitalia, and the internal genitalia are typically female when associated with an ovary or ovotestis and male when associated with a testis. Occasionally, a pubertal patient who was considered male will present with gonadal pain and found to have an ovotestis with a ruptured corpus luteum or have a history of cyclical hematuria corresponding to menses.62 The pathogenesis in some cases of 46,XX ovotesticular DSD is related to RSPO1 gene mutations or SRY.
translocations, or in 46,XY patients, partial deletion of DMRT1, but most cases are unexplained. On microscopic examination, the ovarian tissue usually is normal but the testis shows tubular sclerosis and germ cell loss with age. The arrangement in an ovotestis varies. Wiersma and Ramdial described three main patterns: an outer mantle of ovarian tissue with an inner core of multiple admixed foci of distinct ovarian and testicular tissue; outer mantle of ovarian tissue surrounding distinct compartments of ovarian (at the upper pole) and testicular tissue (at the lower pole) (Fig. 23); and two distinct compartments of ovarian and testicular tissues (Fig. 24), with an interdigitating interface in some.

The risk for a germ cell tumor in ovotesticular DSD is considered low, estimated to be about 3% overall. Germi-nomas are the most frequent but the full spectrum have been reported. A case of IGCNU has been reported in the dysgenetic testis of an 18-year-old 46,XX boy with an SRY translocation to a partially deleted X chromosome. A juvenile granulosa tumor has also been found.

Klinefelter syndrome

This is a common condition estimated to occur in 1 to 500–1000 live births. It is the result of meiotic nondisjunction of the sex chromosomes during gametogenesis and results in a 47,XXY (most commonly) karyotype. Presentation prior to puberty is unusual, but teenagers may present because of gynecomastia, eunuchoid habitus, and poorly developed male secondary sex characteristics. The testis is ordinarily not examined because the diagnosis is made on the basis of clinical, laboratory (elevated gonadotropins), and karyotypic grounds. The testis is characteristically small, averaging 1 cm in greatest dimension. In cases where testicular specimens were examined, they showed germ cell loss with advancing age, tubular hyalinization and shrinkage, tubules lined by Sertoli cells only, peritubular sclerosis, and nodular Leydig cell hyperplasia, the latter secondary to elevated levels of luteinizing hormone. The frequency of gonadal tumors is not increased, but a high proportion (22%) of patients with primary mediastinal germ cell tumors are reported to have Klinefelter syndrome; these tend to occur at a disproportionately young age (15–18 years) and to be nonseminomatous in type.

5α-Reductase deficiency

Patients with this disorder have normal male internal genitalia, which depend on testosterone for development, but lack masculinization of the external genitalia because of deficiency of dihydrotestosterone. They are usually raised as females who most commonly come to medical attention because of masculinization of the external genitalia, sometimes with testicular descent, at the time of puberty. The prepubertal testes are normal in appearance, but regressive changes occur after puberty with varying degrees of tubular sclerosis, diminished to absent germ cells, and Leydig cell hyperplasia with degenerative changes including cytoplasmic vacuolization and apoptosis.

17β-Hydroxysteroid dehydrogenase deficiency

The clinical features of this disorder are similar to those of patients with 5α-reductase deficiency. A disproportionate number of cases have occurred in the Arab population. These genetic males are typically raised as females who undergo virilization at puberty. The testicular morphologic features are also similar. An increased risk of germ cell tumors, estimated at 28%, has been reported but based on only a handful of cases. Additionally, there is an apparent increased risk, calculated at four times elevated, for testicular germ cell tumors in nondeficient populations that have a specific allele of the HSD17B4 gene.
Adrenogenital syndrome

The features of the testicular “tumor” of the adrenogenital syndrome are reported in the article on testicular tumors in this issue. The male patients do not have a disorder of sex development because their genotypic and phenotypic characteristics are congruent, even though they do develop isosexual pseudoprecocity. The female patients who have this syndrome, however, do become virilized and therefore are considered within the spectrum of a DSD. Only one virilized female with the adrenogenital syndrome is known to have developed a morphologically identical lesion to the virilized female with the adrenogenital syndrome. The female patients who have characteristics are congruent, even though they do develop undervirilization syndromes. The late Dr. Robert E. Scully. We also thank Ms. Tracey Bender for her excellent assistance with the preparation of the article.

Other deficiencies in steroid biosynthesis

Numerous other enzymatic deficiencies in the pathway for steroid biosynthesis are associated with disorders of sex development, but they do not show distinct gonadal findings and are not known to be associated with an increased risk of gonadal neoplasms at this time.

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