

AP119 Testicular Tumors: Morphology and Differential Diagnosis

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MORPHOLOGIC ANATOMY OF THE TESTIS

The adult testes are suspended by the spermatic cord and located within the scrotum. The testis proper is surrounded by a thick connective tissue layer called the tunica albuginea which itself is lined by the visceral tunica vaginalis (Fig.1). In the posterior aspect of the gonad is the mediastinum testis that contains blood vessels, lymphatics, nerves and portions of the rete testis. The testis contains multiple fibrous septae which radiate from the mediastinum testis to the tunica albuginea and these divide the organ into approximately 250 compartments which contain the seminiferous tubules.^{1,2} Surrounding the seminiferous tubules is the interstitium which contains Leydig cells, blood vessels, lymphatics and nerves. Each compartment of the testis contains a maximum of four seminiferous tubules which are very convoluted and which usually empty into the straight portion of the rete (tubuli recti). Each seminiferous tubule is lined by a basement membrane and a thin lamina propria. Within the seminiferous tubule are Sertoli cells as well as germ cells at different stages of differentiation.

Sertoli cells comprise 10% to 15% of cells within the tubule. They are columnar to pyramidal in shape with their long axis perpendicular to the basement membrane. The cytoplasm is granular-eosinophilic and may contain fine vacuoles. The nuclei are round-to-oval with finely granular chromatin and are commonly located within a cell or two of the basement membrane. They contain a prominent nucleolus, the only normal cell within the tubule to do so. Intracytoplasmic Charcot-Bottcher crystalloids are characteristic but seen preferentially by electron microscopy.

Sertoli cells have phagocytic capacity but also play an important role in regulating spermatogenesis. By immunohistochemistry they have been shown to express vimentin, cytokeratins 8, 18 and 19, as well as inhibin.^{3,4} Cytokeratin positivity is routinely observed in immature Sertoli cells but expression of this intermediate filament is likely in adults in various conditions including testicular atrophy, Sertoli cell tumors and in Sertoli cells adjacent to germ cell tumors, orchitis and infarct.

Germ cells originate in the yolk sac and migrate to the genital ridge during the first seven weeks of gestation^{5,6}. They comprise 85% to 90% of cells within the seminiferous tubule and have the capacity to differentiate (mature). Spermatogonia are undifferentiated cells located adjacent to the basement membrane. They have clear or basophilic cytoplasm, distinct cytoplasmic membranes, small round nuclei with dark chromatin and no nucleoli. They have the capacity to proliferate and give rise to primary spermatocytes. The latter cells are subclassified into preleptotene, leptotene, zygotene, pachytene and diplotene spermatocytes based on their nuclear chromatin pattern. These subtle differences are difficult, if not impossible, to discern on routine histologic preparations and irrelevant when evaluating tumor-bearing gonads. In general, spermatocytes are larger than spermatogonia, have basophilic cytoplasm, indistinct nuclear borders, round nuclei with distinct chromatin patterns and absent nucleoli. Completion of the first meiotic division gives rise to secondary spermatocytes, which have a short half life and undergo a second meiotic division to form spermatids. Secondary spermatocytes are smaller than their progenitor cell and have denser chromatin. Spermatids are located towards the lumen of the tubule and have small nuclei with dense chromatin. They transform into spermatozoa through metamorphosis.

Leydig cells are present in the interstitium as single cells or in clusters. Interestingly, they may also be observed in the tunica albuginea, mediastinum testis, epididymis and even along the spermatic cord, usually intimately associated to nerve bundles.^{5,7} Leydig cells have abundant eosinophilic cytoplasm and round, regular nuclei with prominent nucleoli. Intracytoplasmic lipofuscin pigment is seen more commonly in older males. Intracytoplasmic Reinke crystalloids are characteristic of Leydig cells, rarely seen in normal cells, and more commonly observed by electron microscopy where they appear as a hexagonal prism.^{8,9}

Leydig cells have the capacity to produce testosterone and share an important paracrine function with Sertoli cells.¹⁰ They express inhibin but not cytokeratins or vimentin by immunohistochemistry.¹¹

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The rete testis collects the effluent from the seminiferous tubules. It is located within the hilus of the testis and includes the tubulae recti, the mediastinal rete and the extratesticular rete. The tubuli recti are short segments within the septa that connect the seminiferous tubules to the mediastinal rete. The mediastinum rete forms a series of epithelial-lined, interconnecting channels that lead to several dilated vesicular channels comprising the extratesticular rete, which anastomose to give rise to the efferent ducts or tubuli efferentia. The epithelium of the rete is low columnar and exhibits luminal microvilli. Every cell contains a flagellum that is not visible by routine light microscopy. The cells are immunoreactive for cytokeratins as well as vimentin.¹²

The efferent tubules have an irregular (undulating) luminal contour. They receive the luminal content from the rete testis and are responsible for resorption of fluid. The epithelial lining is a mixture of ciliated and non-ciliated columnar pseudostratified cells which express cytokeratin and variably vimentin by immunohistochemistry. The epithelial cells are surrounded by a thick basement membrane which in turn is surrounded by a layer of smooth muscle. These tubules lead into the epididymis, a convoluted tubular structure which plays a role in the transport, maturation, and storage of sperm.⁷ Transport is aided by a thick smooth muscle layer that surrounds the epididymis. The epididymis is lined by a thick basement membrane and can be divided anatomically into three sections: head, body and tail, the latter where sperm storage and maturation occurs. The epithelial lining of the epididymis are predominantly tall columnar (principal cells) many of which exhibit esterocilia, but basal cells, clear cells, and luminal cells are also present. The luminal contour of the epididymis is rigid rather than undulating.

The vas deferens arises from the caudal portion of the epididymis which proximally joins the excretory duct of the seminal vesicles to form the ejaculatory duct. The vas deferens is lined by pseudostratified, columnar epithelium and basal cells, the former containing long esterocilia. The luminal contour of the vas is variably folded and the epithelium is surrounded by loose connective tissue and a very thick smooth muscle layer.

Several appendages may be encountered on the testis, testicular adnexae or spermatic cord, the most common being the appendix testis and appendix epididymis.^{13,14} The appendix testis is a vestige of the müllerian duct attached to the tunica vaginalis along the anterosuperior surface of the testis adjacent to the head of the epididymis. It is a small pedunculated structure lined by columnar nonciliated epithelium. The epithelium is undermined by richly vascular connective tissue. The appendix epididymis is a vestige of the mesonephric duct. It is a cystic, pedunculated structure attached to the head of the epididymis. The cyst is lined by low columnar epithelial cells and the external surface is lined by mesothelium. Two other types of appendages are present as incidental findings and represent remnants of mesonephric tubules. They appear as epithelial lined tubular or cystic structures which are seen along the testicular adnexae or spermatic cord. Depending on their location, they are called vas aberrans or paradidymis.^{7,14}

TUMORS OF THE TESTIS

GERM CELL TUMORS

Testicular germ cell tumors (GCT) comprise approximately 98% of all testicular neoplasms and are the most common malignancy in males between the ages of 15 and 35 years.¹⁵ (Table 1) They are relatively uncommon; approximately 5,500 to 6,000 new cases will be diagnosed in the United States during this calendar year. Because of their relative rarity, they present a diagnostic challenge to most practicing pathologist. It is remarkable that tumors of such diverse morphology and clinical behavior should be considered as variants of one entity. Nevertheless, there is circumstantial and laboratory evidence to support this practice. First of all, these tumors tend to arise along the axial skeleton, be it the pineal gland, anterior mediastinum, retroperitoneum or gonads. Secondly, mixed histologic patterns predominate over tumors with one histologic type. A third compelling piece of evidence relates to the so-called precursor lesion. When these tumors arise in the gonad, irrespective of the morphology, one is likely to identify intratubular germ cell neoplasia (IGCN), also known in some circles as *in situ* carcinoma, in the adjacent seminiferous tubules. A fourth important piece of evidence linking these tumors comes to us from genetics, since approximately 80% of tumors, regardless of the primary site and histology, will

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have at least one isochromosome of the short arm of chromosome 12, which is known as i(12p). This genetic abnormality is not pathognomonic of germ cell neoplasia, yet it is a very useful diagnostic tool in selected circumstances due to its rare occurrence in other solid tumors.¹⁶⁻¹⁸

Testicular germ cell tumors can be divided into three groups (infantile/prepubertal, adolescent/young adult, and spermatocytic seminoma), each with its own constellation of clinical histology, molecular and clinical features.^{19,20} They originate from germ cells at different stages of development. The most common testicular cancers arise in postpubertal men, are characterized genetically by having one or more copies of i(12p), and exhibit other forms of 12p amplification and aneuploidy.²¹ The consistent gain of genetic material from chromosome 12 seen in these tumors suggests that it has a crucial role in their development. Intratubular germ cell neoplasia (IGCN) is the precursor to these invasive tumors. Their incidence is approximately 6.0 per 100,000 per year with the majority being discovered between 15 and 40 years of age. Several factors have been associated with their pathogenesis, including cryptorchidism, elevated estrogens in utero and gonadal dysgenesis. Tumors arising in prepubertal gonads are either teratomas or yolk sac tumors, tend to be diploid, and are not associated with i(12p) or with IGNU. The annual incidence is approximately 0.12 per 100,000. Spermatocytic seminoma (SS) arises in older patients. These benign tumors may be either diploid or aneuploid and have losses of chromosome 9 rather than i(12p). Intratubular SS is commonly encountered but IGCN is not. Their annual incidence is approximately 0.2 per 100,000. The pathogenesis of prepubertal GCT and SS is poorly understood.

Intratubular Germ Cell Neoplasia

This term refers to the lesion initially described by Skakkebaek as “carcinoma in situ” as well as to other “differentiated” forms of intratubular germ cell neoplasia.²²⁻²⁵ Strictly speaking, the lesion originally described by Skakkebaek is now called “Intratubular germ cell neoplasia, unclassified” by most, at least in the Western Hemisphere.

The story of testicular “carcinoma in situ”/intratubular germ cell neoplasia is fascinating and serves as a paradigm for the concept of progression from incipient or preinvasive neoplasia to invasive disease.^{24,26,27} In 1972 Skakkebaek reported “atypical spermatogonia” in two men undergoing testicular biopsies during a work-up for infertility who subsequently developed invasive TGCT. He hypothesized that these cells constituted “carcinoma in situ”. Two subsequent seminal studies by his group proved that this was indeed the case. In 1978 he reported a series of 555 men who underwent testicular biopsies for infertility.^{26,27} They identified 6 patients with evidence of “carcinoma in situ”. With a median follow-up period of approximately three years, three of these patients developed evidence of an invasive germ cell tumor; one of them with bilateral disease. The remaining 449 patients were tumor free during the same follow-up period.

In 1986 the Skakkebaek group reported their experience with contralateral biopsies in 500 patients with unilateral GCT.²⁸ Twenty seven patients (5.4%) were found to have “CIS”. Eight patients received systemic chemotherapy for advanced disease. Of the remaining 19 patients, 7 (37%) developed invasive GCT at this site within the follow-up period. Mathematical modeling suggested that 50% of biopsy-positive cases would develop disease within 5 years. Remarkably, not a single case of contralateral GCT developed in the remaining 463 biopsy-negative patients during the same follow-up period. In a subsequent report the authors revealed that at least two of the biopsy-positive cases that received systemic therapy subsequently developed contralateral tumors, suggesting that systemic therapy is not always effective against preinvasive disease.²⁹

It is clear that the original lesion described by Skakkebaek is the precursor to all types of germ cell tumors, at least for those that originate in post-pubertal gonads, other than spermatocytic seminoma. In early 1980, a group of distinguished pathologists including Drs. Robert Scully, Juan Rosai, F.K.K. Mostofi and Robert Kurman met in Minnesota to discuss nomenclature of incipient germ cell neoplasia. They agreed that “carcinoma in situ” was a poor choice to describe this lesion since it had no features of epithelial differentiation. They suggested the term “intratubular germ cell neoplasia, unclassified” (IGCNU) because it was associated with all morphologic types of GCT with the exception of spermatocytic seminoma. It also underscores the fact that differentiated forms of intratubular germ cell neoplasia may occur, including intratubular embryonal carcinoma.

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IGCN can be seen adjacent to invasive germ cell tumors in virtually all cases in which residual testicular parenchyma is present.^{22,30} As previously mentioned, it is present in up to 4% of cryptorchid patients, in up to 5% of contralateral gonads in patients with unilateral GCT and in up to 1% of patients biopsied for oligospermic infertility. Its association with TCGT arising in prepubertal patients is still a source of controversy.^{19,31,32} While some authors suggest that it does not occur, others state that it does. In either case, we can state with reasonable certainty that, if IGCN does occur in childhood tumors, it is certainly less apparent.

IGCNU is characterized morphologically by the presence of enlarged, atypical germ cells located immediately above a usually irregularly thickened basement membrane. The atypical cells are either isolated or form a single row along the basement membrane. They are typically larger than spermatogonia, the other cell that usually resides near the basement membrane. IGCN cells have clear cytoplasm, irregular nuclear contours, coarse chromatin, and enlarged nucleoli which may be single or multiple. On the other hand, spermatogonia may also have clear cytoplasm but the cells are small, have round and regular nuclear contours, densely packed chromatin and absent nucleoli. In most cases, tumor-bearing tubules do not have active spermatogenesis and contain mostly Sertoli cells. Sertoli cells may be displaced towards the tubular lumen. Characteristically they contain a single nucleolus which is small and regular. The nuclei are oval or round with regular borders and the chromatin is fine. The cytoplasm is amphophilic/eosinophilic and not vacuolated.

In essence, the cytologic features of classic IGCN are those of seminoma. The relationship is supported by the coexpression of a host of histochemical and immunohistochemical markers among both cell types. Further evidence comes from electron microscopy which has shown that both share common ultrastructural features including the absence of well developed cytoplasmic intermediate filaments, inconspicuous organelles, glycogen particles, lack of mature desmosomes and cell junctions, and nucleoli with rosy nucleolonema. Tubules whose lumen is filled with these cells may be regarded as "intratubular seminoma".

IGCN may extend into the rete testis, usually undermining the epithelium in a "pagetoid" pattern. Occasionally the epithelium may become hyperplastic and in this setting it is important not to confuse this finding with the presence of nonseminomatous germ cell tumor.

IGCN cells contain glycogen and thus are PAS-positive, diastase-sensitive. Rarely will other intratubular cells, either spermatogonia or Sertoli cells, show similar positivity. Placental-like Alkaline Phosphatase (PLAP) is one of the isoforms of alkaline phosphatase.(Table 2) PLAP antibodies will stain IGCNU as well as the majority of seminomas and embryonal carcinomas as well as a smaller percentage of yolk sac tumors. Immunoreactivity is seen in virtually all cases of IGCN and the staining pattern is usually membranous or cytoplasmic. No other non-neoplastic intratubular cells are immunoreactive for PLAP, but immunoreactivity may be seen in other types of non-germ cell malignancies.³³⁻³⁶ C-kit (CD 117) is expressed in a large percentage of IGCN as well as seminomas, but not in other germ cell tumors.³⁷ Once again, the staining pattern is cytoplasmic/membranous. Despite the overexpression of this antigen, c-kit is rarely mutated in these tumors. Other antibodies which immunoreact with IGCNU but are rarely used in clinical practice include M2A and 43-F.^{36,38,39} POU5F1 (Oct3/4) is a very interesting marker which was recently described.⁴⁰ The gene serves as a transcription factor and its product is expressed in pluripotent mouse and human embryonic stem cells and is down-regulated during differentiation. Since the gene is also required for self-renewal of embryonic stem cells, knocking out the gene is lethal. Early reports suggest that this antigen is expressed solely in IGCNU, seminoma and embryonal carcinoma, suggesting that these are the types of GCT cells with pluripotency, i.e. with capacity to differentiate. In any event, it provides us with yet another marker for IGCNU.

It is important to keep in mind that the presence of neoplastic cells within tubules does not always constitute IGCNU and that one must adhere strictly to the established diagnostic criteria. Besides intratubular seminoma, one can encounter intratubular embryonal carcinoma, intratubular spermatocytic seminoma and even metastatic disease such as melanoma and prostatic carcinoma. Intratubular lymphoma and even mesothelioma may also be confused with IGCNU.

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Seminoma:

Seminomas are the most common germ cell tumors arising in the male gonad, whether they arise in a pure state or mixed with other morphologic types.⁴¹⁻⁴⁷ “Pure” seminoma account for 27%-30% of testicular GCT and another 15%-18% contain syncytiotrophoblasts. Approximately 1% to 2% are bilateral and bilaterality can occur synchronously or asynchronously. Seminomas reach a peak incidence between the 4th and 5th decade of life, which is approximately one decade later than non-seminomatous germ cell tumors.

Macroscopic and microscopic features:

Seminomas appear as a fleshy, well-circumscribed, yellow-tan mass that, depending on size, may occupy a variable amount of testicular parenchyma or replace it entirely. Areas of necrosis may be observed grossly in up to 20% to 25% of cases. Some seminomas are associated with a granulomatous reaction, and in these cases the tumor takes on a fibrous and nodular gross appearance. Microscopically, tumor cells are uniform and have round to vesicular nuclei with clear cytoplasm, prominent cytoplasmic membranes and a centrally-located, round nucleus with a prominent nucleolus. These cells are arranged in sheets or nests separated by thin fibrovascular bands which contain mature lymphoid cells. Mitotic activity is variable. Some cases exhibit extensive fibrosis, particularly those associated with a granulomatous reaction or tumors that have undergone partial regression. Rarely seminomas may exhibit unusual patterns such as cribriform, pseudoglandular, and tubular growth.⁴⁸ These do not represent separate entities, but rather histologic variants of classic seminoma. Less than 20% of cases contain syncytiotrophoblasts, but their presence may be associated with focal areas of hemorrhage and necrosis. Seminomas with syncytiotrophoblasts will be accompanied by serum elevation of human chorionic gonadotropin (HCG), but levels will rarely reach above 500 iu/ml.⁴⁷

Tumor cells contain glycogen (PAS positive) and express Placental Alkaline Phosphatase (PLAP) and c-kit (CD-117) by immunohistochemistry,^{33,34,49-55} but not cytokeratins, CD-30 or inhibin. A minority of seminoma cells may express focal and weak, dot-like or linear immunoreactivity for cytokeratin; however, never diffuse and strong staining throughout the cytoplasm. Like IGCN, seminoma cells express POU5F1 (Oct 3/4) in a nuclear distribution.^{33,37,56,57} (Table 2)

Some seminomas exhibit a significant degree of cytologic atypia⁵⁸⁻⁶⁶ and this fact led to the now abandoned concept of “Anaplastic Seminoma” as a discreet entity with a worse prognosis.^{67,68} As described this tumor was characterized by overall morphologic features of a seminoma but containing more pleomorphic cells with non-clear cytoplasm and abundant mitotic figures. Fibrovascular septae and lymphocytes were absent and focal necrosis was commonly seen. This concept did not withstand the test of time since many series later showed that stage for stage there was no difference in clinical outcome between classic and anaplastic seminomas.^{43,58,69} In addition, it has become quite evident that mitotic activity in seminomas is quite variable and, in fact, may be quite high even in classical cases.⁶⁰ Presently tumors thought to be seminoma but exhibiting atypical histology should trigger consideration of a differential diagnosis of seminoma which includes a) seminoma with “early carcinomatous differentiation”, b) solid variants of embryonal carcinoma or yolk sac tumor, c) lymphoma, d) sex-cord gonadal stromal tumor, and e) metastatic disease, including poorly differentiated carcinoma and melanoma. Other causes of atypical histology in seminoma include poor fixation and faulty processing in the pathology laboratory. “Early carcinomatous differentiation” refers to areas of transition from seminoma to embryonal carcinoma. This concept suggests that seminoma cells are not terminally differentiated but rather, under certain poorly understood circumstances, may differentiate into other germ cell tumor-types.^{47,63,70}

Spermatocytic Seminoma

Spermatocytic seminomas are rare, comprising less than 2% of testicular neoplasms.^{47,71,72} In fact, in our institution they account for significantly less than 1% of primary testicular tumors resected. Although classified as a variant of seminoma, in reality they represent an entirely separate and distinct clinicopathologic entity. The peak incidence is in the sixth decade of life; however, occurrence in younger patients as early as the third decade of life is reported. This tumor occurs only in the male gonad, may be

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unilateral or bilateral, and is not associated with cryptorchidism. It is a benign tumor with only one documented case having metastasized. An exception to this rule is the rare case of "Spermatocytic seminoma with sarcoma".^{73,74} These very rare tumors exhibit an undifferentiated or differentiated sarcoma component and are commonly associated with metastatic disease at the time of initial diagnosis. Prognosis is poor. Median survival is less than one year with patients dying of widely metastatic disease.

Gross and microscopic features

Spermatocytic seminoma may be large, nodular, and may have a myxoid, mucoid or fleshy appearance. Areas of hemorrhage, cystic degeneration, and necrosis are common. Microscopically, tumor cells are arranged in solid sheets or nests of round cells. Occasionally the tumor cells may be arranged in nests or pseudoglandular arrangements within an edematous or mucoid stroma. Cytologically, it is possible to identify three distinct cell types; small, medium and large although cells of intermediate size predominate. The intermediate cells have a small amount of eosinophilic or amphophilic cytoplasm. The nuclei are round and contain coarse chromatin, at times exhibiting a "spireme" (filamentous or string-like) pattern. The small cells have dark staining nuclei and scant eosinophilic cytoplasm. The large cells have giant round or oval nuclei with a classic spireme chromatic distribution. All three cell types may be present within seminiferous tubules (intratubular spermatocytic seminoma). Mitoses are frequent, including atypical forms. These tumors rarely contain a lymphocytic infiltrate and are not associated with a granulomatous reaction.

Tumor cells do not contain glycogen (negative PAS stain). Immunohistochemical stains for PLAP are negative, although occasional cells may be weakly immunoreactive. Cytokeratins are negative, although occasional cells may exhibit dot-like cytoplasmic staining. CD-30 is negative, while some investigators have reported immunoreactivity for CD-117 (c-kit).^{37,47,75,76} (Table 2)

Embryonal Carcinoma

Embryonal carcinomas comprise up to 3% of pure GCT, although it is a common component of mixed germ cell tumors. It rarely presents as pathologic stage I disease and is not associated with elevation of HCG or alfafetoprotein (AFP).^{43,47}

Gross and microscopic features

Embryonal carcinomas (EC) may vary in size, color, and texture, are commonly hemorrhagic, and exhibit areas of cystic degeneration and necrosis. Microscopically, tumor cells are large, irregular, and epithelioid. They exhibit scanty cytoplasm, large pleomorphic nuclei with coarse chromatin, and multiple irregular nucleoli. Common findings include nuclear overlap, individual cell necrosis, and apoptotic bodies. The pattern of growth is quite variable: gland-like, papillary, syncytial, and solid areas are commonly encountered. The solid variant of EC may be confused with "atypical" forms of seminoma, although the latter does not exhibit the same degree of cytologic anaplasia as embryonal carcinoma. Immunohistochemistry is useful in resolving this differential diagnosis. Embryonal carcinoma may have overlapping morphologic features with yolk sac tumor (YST) but, once again, close attention to subtle cytomorphologic differences and immunohistochemistry will resolve the majority of cases. Most ECs are immunoreactive for PLAP, low molecular weight cytokeratins, CD-30 and POU5F (Oct 3/4). They do not express CD-117, AFP or HCG.^{37,76} (Table 2)

Large cell lymphoma and metastatic poorly differentiated carcinoma may also enter in the differential diagnosis. ECs are said to be negative with immunohistochemical stains for Epithelial Membrane Antigen (EMA), Carcinoembryogenic Antigen (CEA), and B72.3.⁷⁷ All may be expressed in a subset of poorly differentiated non-germ cell carcinomas. Depending on the cell of origin, large cell lymphomas will be immunoreactive for B or T cell markers.^{33,34,49-51,53-55}

Yolk Sac (Endodermal Sinus) Tumor

Yolk sac tumors (YSTs) are characterized by multiple patterns of growth that recapitulate the yolk sac, allantois, and extra embryonic mesenchyme. It has a bimodal age distribution; infants and young children

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and postpubertal males. In the latter group, it rarely presents in a pure form but is present in almost half of mixed germ cell tumors.⁴⁷ In children it commonly presents in its pure form, usually within the first two years of life. These tumors are associated with serum elevation of AFP in the overwhelming majority of cases.

Gross and microscopic features

The gross appearance of YSTs is quite variable because YST components are usually closely admixed with other elements. If pure, they commonly appear grey-white with a myxoid or even mucoid appearance. Areas of hemorrhage and geographic necrosis are common. Microscopically these tumors are quite variable due to the multiple subtypes which are usually intermixed:^{44,78}

- Endodermal Sinus (Schiller-Duval): This pattern exhibits Schiller-Duval bodies that are perivascular arrangements of cuboidal or low columnar epithelial cells with an intervening "labyrinth-like" network of extracellular spaces. This pattern is quite distinctive and recognized by most pathologists. Unfortunately, it is seen in only a minority of tumors.
- Reticular or microcystic: It is the most commonly encountered pattern and is characterized by round to oval tumor cells with variable amounts of cytoplasm surrounded by cysts. These cysts vary in size and may contain an amorphous eosinophilic or basophilic fluid.
- Papillary
- Glandular-alveolar
- Myxomatous: This pattern is quite common and characterized by cords or nests of neoplastic cells embedded in a stroma rich in hyaluronic acid. This pattern is most commonly seen adjacent to microcystic and solid areas.
- Enteric
- Macrocystic
- Polyvesicular vitelline
- Hepatoid
- Solid: This pattern may be confused with other germ cell tumors, particularly seminoma.

Tumor cells of YST are not as primitive or pleomorphic as those seen in EC. They have more abundant clear or weakly granular cytoplasm, which is often vacuolated. Individual cell necrosis and apoptotic bodies are not as conspicuous as in EC. The cytoplasm may contain small, spherical, and densely eosinophilic intracytoplasmic droplets that are PAS positive and diastase resistant. These represent either AFP or, more commonly, alpha-1-antitrypsin deposition. Cells may be spindle or stellate, making them easily confused with mesenchyme. The extracellular matrix adjacent to YST is myxomatous, a feature which is rarely seen in EC.

Tumor cells of YST are usually immunoreactive for AFP, and low molecular weight cytokeratins. PLAP staining is variable and may be absent. CD117 (c-kit) and CD-30 are usually negative as is Oct 3/4.³⁷
33,34,49-51,53-55 (Table 2)

CHORIOCARCINOMA:

Choriocarcinoma is composed of syncytiotrophoblastic, cytotrophoblastic, and other trophoblastic cells. It comprises less than 1% of testicular GCT in its pure form; however, may be encountered as a component of a mixed GCT in up to 10% of cases.^{43,47,79} In its pure form, these tumors occur in the second and third decades of life, are commonly associated with very high levels of serum HCG, and exhibit metastatic disease at the time of initial presentation. Small foci of choriocarcinoma within a mixed germ cell tumor do not alter the prognosis.

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Gross and microscopic features

These tumors usually present as a hemorrhagic, necrotic mass with evidence of fibrosis and regression in some instances. Microscopically these tumors exhibit an admixture of trophoblastic cells in varying proportions. Most cases will have syncytiotrophoblasts and cytotrophoblasts with occasional intermediate trophoblastic cells present. The tumor cells are usually associated with hemorrhage and necrosis that may be so abundant that many surgical sections are required to see any viable disease. Very rare cases exhibit few syncytiotrophoblasts, containing predominantly cytotrophoblasts and intermediate trophoblastic cells. These tumors have descriptively been called “monophasic” variants of choriocarcinoma, have no association to a distinct clinical meaning, and are more likely encountered in the post-chemotherapy setting.^{80,81} Another recently described and even rarer variant of trophoblastic disease is called Placental-site trophoblastic tumor.⁸² It is composed of intermediate trophoblastic cells exclusively. These cells are mononuclear, pleomorphic and exhibit eosinophilic cytoplasm. They are immunoreactive for Human Placental Lactogen (HPL) and cytokeratins.

Syncytiotrophoblasts are immunoreactive with HCG as well as inhibin, epithelial membrane antigen, and low molecular weight cytokeratins. PLAP may be positive but staining is variable.⁴⁷ (Table 2)

TERATOMA:

The term teratoma refers to neoplasms composed of tissues which have differentiated along any of the three somatic pathways: ectoderm, mesoderm, or endoderm.^{43,44,47} Tumors composed of only one of these components are regarded as monodermal teratomas. Teratomas may be composed of mature tissues, embryonal-type tissues, or a mixture of both. Historically they were subclassified as immature and mature forms based on their degree of differentiation. The World Health Organization now recommends that these morphologies be considered as a single entity based on their overlapping genetic features.

Teratomas have a bimodal incidence peak. They represent approximately a third of tumors in children and are benign. In adults, the incidence of pure teratoma is less than 7%. It is commonly found as a component of mixed GCT in adults. Teratomatous components may be the only remaining recognizable tumor after spontaneous regression or after systemic therapy.

Gross and microscopic features

Tumors are usually heterogeneous, firm, nodular, and well circumscribed. They may be solid or cystic depending on its histologic components. Histologically, they may contain mature elements such as neural, glandular, and squamous tissues. Attempts at organ formation are common, particularly in children. Mesenchymal components such as smooth muscle cartilage are also common. Fetal-type tissues can emerge from any histologic type. Characteristically, all components — whether mature or fetal — are intermixed. When one of the teratomatous components, whether mesenchymal (skeletal muscle), neural (primitive neuroepithelium) or epithelial (glandular or squamous), predominate and form an “expansile” mass, the term “teratoma with somatic type malignancy” is used.^{47,83-87} These tumors were originally coined “teratoma with malignant transformation”, a term no longer in use. The definition of what constitutes somatic type malignancy is controversial but most authors suggest that the expansile nodule should be equal or greater than a 4X microscopic field. The incidence of secondary somatic malignancy is approximately 3%. This phenomenon may be seen de novo in testicular GCT, more commonly in mediastinal primaries, and in retroperitoneal disease resected after chemotherapy.^{84,85} If limited to the gonad it is not associated with a worse prognosis; the reverse is true when encountered in other sites.

Tumors of more than one histologic type

Mixed germ cell tumors comprise between 35% and 54% of GCT, exclusive of seminomas with trophoblastic cells and spermatocytic seminoma with sarcoma.^{43,47} They are rarely seen in prepubertal gonads. Cases containing a component of seminoma tend to occur later in life than those that do not. All the morphologic variants previously described may be encountered with the exception of spermatocytic seminoma. As expected, the gross and microscopic features are quite variable and will depend on the

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histologic components encountered. The term “teratocarcinoma” should be avoided since it lacks diagnostic specificity.

Epidermoid cyst

Epidermoid cysts constitute 1% or less of all testicular neoplasms.^{47,88,89} Their histogenesis is unclear, although most investigators suggest that they represent monodermally differentiated mature teratoma, supported by the fact that a recent case with adjacent IGCNU was identified.⁹⁰ Some have suggested that they arise from inclusion cysts, while others propose squamous metaplasia of seminiferous tubules or the rete testis (tumor-like condition). They are commonly discovered between the second and fourth decades of life and are often asymptomatic. These tumors may be as large as 10 cm although most measure less than 2 cm.

Grossly they appear as well-circumscribed cystic masses filled with keratinized debris similar to an epidermal inclusion cyst. The cyst wall is composed of fibrous tissue surrounding flattened squamous epithelium. No dermal adnexal elements or other teratomatous elements are present in the cyst wall or surrounding testicular parenchyma. These tumors are not associated with a testicular scar; furthermore, IGCN is not present except for in the above-mentioned case.

These unusual neoplasms are invariably benign and should be managed conservatively. Nevertheless, the lesion should be thoroughly sampled and examined by the pathologist to rule out other elements of IGCNU.

Dermoid cysts have been described in the testis and are characterized by the presence of squamous epithelium overlying skin appendages.^{91,47} Occasionally other teratomatous components may be present. They are considered a benign variant of cystic teratoma analogous to what is seen in the ovary. They are extremely rare and by definition are not associated with IGCNU.

COMPLETELY OR PARTIALLY “BURNED OUT” GERM CELL TUMOR

A possible explanation for most — if not all — presumed “primary” retroperitoneal GCT lies in the concept of partially or completely “burned out” germ cell tumor. For many decades, pathologists have observed areas of regression within germ cell tumors. These usually take the form of a well defined stellate fibrous scar at the periphery where sclerosed seminiferous tubules are evident.⁹²⁻⁹⁴ The scar may be accompanied by a sparse plasma cell infiltrate and aggregates of hemosiderin and macrophages may be present. The scar is usually located well within the substance of the testis. It may abut the mediastinum testis but is rarely located towards the poles or directly below the tunica albuginea. The latter location suggests the possibility of a post-traumatic scar. Another occasional feature seen in burned out lesions is the presence of peculiar hematoxyphilic deposits having an amorphous or granular structure. These deposits appear to be located within hyalinized seminiferous tubules. Infrequently, these hematoxylin staining bodies may be associated with scattered malignant germ cells. A burned out lesion without any viable GCT may be the only evidence of a regressed testicular primary. If viable germ cell components are present, they usually are in the form of teratoma, seminoma, or IGCN. Burned out lesions may be very small, rendering them nonpalpable; nevertheless, they are usually discernible by testicular ultrasound.

Pathologic Prognostic Factors in Stage I Nonseminomatous Germ Cell Tumors (NSGCT)

Until recently, the treatment of choice for stage I NSGCT was radical orchiectomy followed by retroperitoneal lymph node dissection (RPLND). Given the advent of highly effective chemotherapy, the availability of sensitive serum tumor markers, as well as more precise staging techniques, orchiectomy alone followed by close surveillance is a viable option for some patients. Overall, 20%-25% of patients treated in this manner will recur, usually in the retroperitoneum and within a year of the orchiectomy. Many studies have shown that the presence of vascular invasion (VI) in the primary tumor is the best predictor of recurrence. In fact, the importance of vascular invasion in the primary is reflected in the TMN classification.(Table 3) The impact of tumor histology on future relapse remains controversial but most authors have suggested that a pure or predominant EC component also is more likely metastasize.⁹⁵⁻⁹⁷

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SEX CORD-STROMAL (GONADAL STROMAL) TUMORS OF THE TESTIS

Sex cord-stromal (gonadal stromal) tumors are rare, comprising approximately 4.0% of testicular neoplasms. (Table 1) Similar tumors may arise in the female gonads. The term refers to neoplasms containing Leydig (interstitial) cells, Sertoli cells, granulosa cells, or theca cells. Tumors may be made up of one or a combination of these cell types in varying degrees of differentiation. The terminology used to describe these tumors is confusing and controversial but it is best to adhere to the classification set forth by the World Health Organization (Table 1).

Leydig (Interstitial) Cell Tumor

Leydig cell tumors (LCT) are the most common pure testicular sex cord-stromal neoplasm and account for 1% to 3% of testicular neoplasms. They may occur at any age, though most common between the third and sixth decades of life.^{43,47,98-100} Fifteen to twenty percent of cases will present in prepubertal children. Approximately 10% will metastasize with metastasis occurring at an older age. LCTs usually arise in normally descended testes although they have been described in cryptorchid gonads as well as in testes that have undergone orchiopexy. Only three cases have been reported in patients with Klinefelter's syndrome.

Most, if not all, children with LCT present with isosexual precocity, which is characterized by deepening of the voice, appearance of body hair, penile enlargement and advanced bone age. Often these physical changes are accompanied by excessive aggression or shyness. LCT must be considered in the differential diagnosis in all prepubertal patients with a testicular mass and precocious puberty. Painless testicular swelling is the most common manifestation in adults, followed by bilateral gynecomastia. It is not unusual for gynecomastia to precede the appearance of a testicular mass and in 15% of cases the former is the only complaint at initial presentation. Approximately 25% of patients with gynecomastia experience a decrease in potency or libido. Given the low incidence of these tumors, endocrinological studies are limited and incomplete. Prepubertal patients will usually have elevated serum testosterone as well as elevated urinary 17-ketosteroids. In adults, elevated estrogen levels have been documented in patients with, as well as without, gynecomastia. Testosterone levels may be low or normal in patients with gynecomastia and high levels of serum estradiol.

Gross and microscopic features

Grossly, LCT is a well-circumscribed, yellow-tan or brown-gray lobulated mass occasionally containing fibrous septae. Macroscopic evidence of hemorrhage or necrosis is rare. Microscopically, the tumor is made up of large polyclonal cells with abundant eosinophilic and granular cytoplasm. Less frequently, the cytoplasm may be clear or vacuolated or microcystic.^{101,102} Nuclei are round or vesicular with delicate chromatin and a single prominent nucleolus. The cells usually exhibit a solid pattern of infiltration although fibrous septae may give them a pseudotubular or trabecular appearance. Crystalloids of Reinke are present in 25% to 40% of cases but may require electron microscopic examination for their identification. On light microscopy they appear as densely eosinophilic needle-like or rhomboid structures within the cytoplasm. LCT are likely to be immunoreactive with inhibin and vimentin but not cytokeratins, CD-30, Oct 3/4, or PLAP.^{47,103-106} (Table 2)

It is difficult to determine histologically those tumors which will metastasize. Kim et al. reported their experience with 40 cases as well as reviewed the literature and confirmed that tumors larger than 5 cm as well as those with infiltrative margins, vascular invasion, nuclear atypia, or increased mitotic rate were associated with aggressive behavior.⁹⁸ Interestingly, none of the malignant cases presented with endocrine manifestations or occurred in prepubertal children. Cheville et al. found that malignant Leydig cell tumors were more likely to high proliferation rate and to be nondiploid.¹⁰⁷ The most common metastatic sites are retroperitoneal and inguinal lymph nodes followed by the lungs and liver.

LCT must be distinguished from Leydig cell hyperplasia or nodular aggregates of Leydig cells which occur in atrophic testes (including patients with Klinefelter's syndrome) and in testicular parenchyma adjacent to

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germ cell neoplasia. Here Leydig cells infiltrate between seminiferous tubules without displacing or obliterating them. LCT must also be distinguished from other sex cord-stromal tumors, especially when the former exhibits a cord-like or tubular pattern which may mimic a Sertoli cell tumor. Secondary lesions such as lymphoma, malignant melanoma, and poorly differentiated carcinoma may also enter in the differential diagnosis. LCT with microcystic features may be confused with yolk sac tumors.¹⁰¹ Similarly, one must not confuse LCT with malakoplakia or with the bilateral testicular masses seen in patients with untreated adrenogenital syndrome.

A lesion that must not be confused with LCT is that which occurs in association with congenital adrenal hyperplasia (CAH, tumor of the adrenogenital syndrome).^{43,47,108} CAH is due to a defect of any one of five enzymatic steps involved in steroid synthesis. This disorder is an inborn error of metabolism, has an autosomal recessive mode of inheritance, and is the most common cause of ambiguous genitalia in infants. 90% to 95% of cases are due to 21-hydroxylase deficiency. A small percentage may be due to 11-B-hydroxylase, 3-B-hydroxysteroid, 17-a-hydroxylase, or cholesterol desmolase deficiency.

Persistent stimulation of adrenal cortical tissue by ACTH may give rise not only to hyperplasia, however, rarely to adrenal cortical neoplasia (both adenomas and carcinomas). Heterotopic or accessory adrenal cortical tissue can also become hyperplastic and enlarged. A testicular "tumor" of adrenal cortical type is defined as a tumefactive lesion of uncertain histogenesis in the setting of CAH which histologically resembles hyperplastic adrenal cortical cells stimulated by ACTH and in which endocrinological evaluation may reveal ACTH-dependency. These tumors are thought to arise from primordial rests within the testicular hilum. These rests are a collection of cells morphologically resembling Leydig cells and found in a large proportion of cases of well-studied CAH. Nodules of these cells may be clinically undetectable or demonstrated only through testicular ultrasound. Larger "tumors" are usually associated to undiagnosed cases of CAH or with patients who have demonstrated poor compliance with their treatment.

Testicular "tumors" in CAH usually occur in early adult life (average age of 22.5 years). Smaller tumors are seen in younger patients, typically located in the hilum of the testis. In adults, the lesions may measure up to 10.0 cm. Eighty three percent of tumors are bilateral. In contrast, LCTs are bilateral in 3% or less of cases. The lesions are unencapsulated and are light tan-brown in color due to the absence of lipids and the presence of cytoplasmic lipochrome pigment. They are usually lobulated as a result of the presence of prominent bands of fibrous connective tissue. Occasionally, multiple extratesticular nodules measuring up to 1.5 cm. in diameter have been described along the spermatic cord or adjacent to the epididymis. Microscopically, there are sheets and nests of cells with abundant granular cytoplasm and relatively distinct cell borders. Nuclei are uniform, round-to-oval with one or two prominent small nucleoli. Many of the tumor cells contain lipochrome pigment (lipofuscin). Mitoses are very uncommon.

As you might imagine from the microscopic description, there is great resemblance to Leydig cells. Indeed, Leydig cell tumor is the most common diagnosis made in these cases. Reinke crystals have not been described in tumors of CAH; however, are seen in up to 40% of LCT. Ultrastructurally, the cells have features of steroid producing cells with abundant smooth endoplasmic reticulum, numerous mitochondria, and accumulation of lipofuscin. The mitochondrial cristae may be lamellar or have a vesicular profile.

Sertoli Cell Tumor

Sertoli cell tumors (SCT) are rare, comprising less than 1% of testicular neoplasms.^{43,47,99,109,110} They were first described in the testis by Teilum who recognized their histologic similarity to Sertoli cell tumors of the canine testis. They may occur at any age and approximately 15% develop in children. Patients characteristically present with a painless mass in a normally descended testis. Gynecomastia is evident in one third of patients. Hormonal alterations in patients with SCT have been poorly documented. Nevertheless, SCT should be in the differential diagnosis of all prepubertal patients presenting with a testicular mass and gynecomastia. Three cases have been reported in boys with Peutz-Jeghers syndrome.¹¹¹

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Gross and microscopic features

Grossly, SCT are well circumscribed, solid and yellow-white or tan. The lesions may be lobulated and may contain small areas of hemorrhage. Microscopic examination reveals mostly tubules but also cords, nests, and masses of tumor cells in a fibrous stroma. The neoplastic cells may contain abundant intracytoplasmic lipid giving them a clear or vacuolated appearance. Electron microscopy may reveal Charol-Bottcher filaments within the cytoplasm that are characteristic of Sertoli cells. The classification of SCT should be reserved for tumors composed entirely of Sertoli cells. Those neoplasms composed only partially of these cells should be classified as mixed or incompletely differentiated sex cord-stromal tumors. SCT are immunoreactive for inhibin, vimentin and cytokeratins.¹¹⁰ (Table 2) Markers typically seen in GCT are negative.⁴⁷

Metastases will occur in approximately 10% of SCT.^{110,112} Metastases are usually to inguinal or retroperitoneal lymph nodes, although skin and pulmonary involvement have been reported. Due to the rarity of this tumor, histologic criteria associated with malignant behavior are unreliable. The presence of metastasis remains as the best indicator of malignancy.

SCT must be distinguished from non-neoplastic, hyperplastic nodules of seminiferous tubules lined by Sertoli cells. These Sertoli cell nodules were mistakenly previously referred to as adenomas. They may contain central hyaline material resembling Call-Exner bodies or laminated calcifications. The nodules are usually small and are most frequently encountered in cryptorchid testes, in atrophic scrotal testes, or adjacent to germ cell tumors. SCT are distinguished from other sex cord-stromal tumors by the predominantly tubular pattern in the former.

Radically orchiectomy is the treatment of choice and will be curative in the majority of cases. Since only 10% of cases will develop metastasis and no reliable criteria exist to predict an increased risk of metastasis, the role of primary retroperitoneal lymph node dissection is controversial. The role of radiation therapy and chemotherapy in patients with metastatic SCT is uncertain.

In 1980, Proppe and Scully described a subtype of SCT which they called **Large Cell Calcifying Sertoli Cell Tumor (LCCSCT)**.^{113,114} It usually presents during the first three decades of life although cases in older males have been described. While patients may present exclusively with a testicular mass, their initial symptomatology could be related to other associated conditions such as pituitary adenomas, bilateral adrenocortical hyperplasia, cardiac myxomas, or other sex cord-stromal tumors. Approximately one third of LCCSCTs are bilateral and some will metastasize.¹¹⁵ These tumors are usually less than 5 cm in size and microscopically are characterized by large polygonal cells with abundant eosinophilic cytoplasm in a fibrous or myxoid stroma. Tumor cells within seminiferous tubules are present in 50% of cases. Microcalcifications are usually abundant. LCCSCTs are often mistaken for LCT but the abundant calcifications, frequent intratubular growth, absence of Reinke crystals, and unusual clinical associations should direct us towards the correct diagnosis.

Granulosa Cell Tumor

The adult variant of Granulosa cell tumor very rarely develops in the testis.^{99,100,116,117} They have been described in males between the ages of 21 and 73 years who presented with testicular mass and gynecomastia. Urinary estrogen levels may be elevated. The tumors measure up to 13 cm in greatest diameter and microscopically are composed of neoplastic cells in a microfollicular and diffuse infiltrative pattern. The cells have scanty cytoplasm and angular, pale nuclei with longitudinal grooves. Call-Exner bodies may be evident in the microfollicular areas. Metastases are rare.

Granulosa cell tumors analogous to juvenile granulosa cell tumors of the ovary are the most common sex cord-stromal tumor of the infantile testis.^{43,118,119} They are usually present in the first six months of life, the oldest reported case being in a 21-month-old. Two cases have developed in undescended testes. Juvenile granulosa cell tumors may arise in patients with an abnormal karyotype and ambiguous genitalia. Tumors may be solid, cystic or both and the cysts frequently contain a gelatinous material. Microscopically, the tumor exhibits either a follicular or solid pattern and the cells are characterized by a

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moderate to large amount of eosinophilic cytoplasm and hyperchromatic nuclei. Stromal hyalinization is often extensive. Although mitoses may be plentiful, no testicular tumor of this type has metastasized.^{47,120}

Sex cord-gonadal stromal tumors, mixed or incompletely differentiated forms

As you might expect, these two categories include tumors with more than one identifiable sex cord-stromal element as well as tumors in which the exact gonadal stromal cell of origin cannot be established with certainty.^{43,47,121} These neoplasms may occur at any age although more than half of the patients are either children or infants. Painless testicular enlargement is the most common presenting symptom, which is infrequently associated with gynecomastia. Grossly, these tumors are similar to other sex cord-stromal neoplasms and their microscopic appearance is quite variable, ranging from predominantly epithelioid to predominantly stromal growth patterns. Frequently the cells are undifferentiated making precise classification impossible. Approximately 30% of tumors presenting in patients older than 10 years of age are malignant while tumors presenting in younger patients follow a benign course. Histologic predictors of aggressive clinical behavior have not been established. Radical orchiectomy is the treatment of choice while retroperitoneal lymph node dissection should be given serious consideration in patients older than 10 years of age.

Tumors Containing Both Sex Cord-Stromal and Germ Cell Elements

Gonadoblastoma:

Gonadoblastomas are rare neoplasms composed of sex cord elements intimately admixed with germ cells.^{47,121} These tumors generally arise in chromosomally abnormal individuals with dysgenetic gonads; 20% of cases occur in phenotypic males. Patients usually present with cryptorchidism, hypospadias, and internal female genitalia, although two cases have been reported arising in a scrotal testis. One third of cases are bilateral and 60% are associated with malignant germ cell elements that are usually seminoma but may be yolk sac tumor or embryonal carcinoma. While gonadoblastomas do not metastasize, metastasis from the associated germ cell tumor may occur.

The microscopic appearance is distinctive and consists of tumor nests surrounded by connective tissue stroma. The nests contain germ cells with clear cytoplasm and sex cord elements resembling Sertoli cells, granulosa cells or both. The nests may contain hyalinized eosinophilic structures resembling Call-Exner bodies.

Since gonadoblastomas are frequently bilateral, excision of the contralateral gonad is mandatory. If there is an associated germ cell tumor, the patient should be carefully worked-up for metastatic disease.

Germ cell/sex cord-gonadal stromal tumor, unclassified

This is a controversial entity which is also composed of an admixture of germ cells and sex cord-stromal elements but which occurs in phenotypically and genotypically normal males.^{47,109,122,123} To date, there have been no endocrine abnormalities described with this lesion. The tumor may be large, measuring up to 12 cm in diameter. It is usually solid, gray-white and well-circumscribed. Microscopic examination reveals an admixture of germ cells and sex cord-stromal elements not arranged in nests, but instead, having a trabecular, tubular, or haphazard infiltrative pattern. However, recent data questions whether the germ cell component is neoplastic, in part due to the fact that the germ cells lack immunoreactivity for PLAP and CD117.¹²⁴

Miscellaneous tumors

Tumors may arise within the rete testis, epididymis, mesothelial lining of the tunica vaginalis, as well as the soft tissues surrounding the testicular hilum and spermatic cord. Hematopoietic tumors as well as metastatic lesions may also be encountered. These entities are beyond the scope of this chapter and the readers are directed to recent authoritative reviews on these subjects.^{43,47}

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TUMORS OF THE TESTICULAR ADNEXA AND PARATESTICULAR TISSUES

The majority of testicular tumors are of germ cell origin, followed by gonadal-stromal neoplasms. Nevertheless, other neoplasms do occur and, due to their rarity, often present diagnostic dilemmas. It is beyond the scope of this presentation to discuss all intrascrotal lesions, but rather we will focus on selected lesions that may present as intrascrotal masses and cause diagnostic challenges.

Lesions of the Rete Testis: Hyperplasia, Adenoma and Adenocarcinoma:

Hyperplasia of the rete testis is a common, usually incidental finding and may be associated with many conditions, including testicular atrophy and as a reaction to adjacent intragonadal neoplasms such as germ cell tumors.¹²⁵⁻¹²⁸ It has been associated with other conditions such as chronic hepatic insufficiency and renal dysplasia. Microscopically it is characterized by proliferation of the rete epithelium which forms exaggerated tubulopapillary channels which are interconnecting. The lining epithelium is composed of cuboidal to low columnar cells with banal nuclear cytology. The interanastomosing channels may become cystically dilated but usually merge with normal appearing rete testis. It is important to recognize hyperplasia of the rete when it is associated with germ cell tumors. For example, hyperplastic rete may be confused with a nonseminomatous component in cases of pure seminoma, leading to not only an inaccurate diagnosis but also to improper therapy. Clues to the correct diagnosis lie in the benign nuclear cytology of the hyperplastic rete epithelium and its close association to normal rete testis. Hyperplasia of the rete may also be seen in association to pagetoid spread of in situ germ cell neoplasia. Once again this phenomenon should not be confused with a nonseminomatous germ cell tumor. In other circumstances the hyperplastic rete testis epithelium associated with an invasive germ cell tumor may exhibit intracytoplasmic eosinophilic hyaline globules which likely represent absorbed proteinaceous material. In these cases one should not mistake this finding with yolk sac tumor.

Benign tumors of the rete testis have been described rarely and these have run the spectrum of adenoma, cystadenoma and cystadenofibroma, depending on their cellular components.¹²⁶ A distinctive variant has been called Sertoliform Cystadenoma. These circumscribed lesions have measured up to 3 cm in greatest diameter and contain benign appearing columnar tumor cells with basally located nuclei and prominent, regular nucleoli. If associated with a sclerotic stroma the tumor cells may be seen as cords or thin trabeculae. It should be blatantly apparent that this particular lesion may be very difficult to differentiate from a sertoli cell tumor, this observation being more acute since at least one case of sertoliform cystadenoma of the rete testis has been shown to be immunoreactive for inhibin.¹²⁷ The correct diagnosis can be made if transition with hyperplastic or normal rete epithelium is present.

Carcinoma of the rete testis is extremely rare with less than 40 bona fide cases described in the literature.^{125,129} In fact, many of the cases may well represent other tumors confused with carcinoma arising in the rete. Lesions that must be considered in the differential diagnosis include a). metastatic carcinoma, b). mesothelioma, and c). ovarian-type carcinoma. Before accepting a tumor as a primary carcinoma of the rete testis, the following conditions must be met.

- Tumor centered in the hilum of the testis. This may be difficult to assess in masses of considerable size.
- Transition from normal to neoplastic rete epithelium. Once again, this may be difficult to ascertain in large lesions that have destroyed the normal anatomy of the testicular hilum. One must also be cognizant of the fact that other tumors such as those of germ cell and mesothelial origin may involve the rete secondarily.
- Absence of a primary elsewhere with similar histology.
- Morphology incompatible with any other intratesticular, adnexal or scrotal primary.
- Proper immunohistochemical panel excluding other primaries.

Rete testis carcinoma has been described in all ages but it is classically a tumor of adults with a peak incidence in the seventh decade of life. Most patients present with unilateral painful testicular swelling, with or without an associated hydrocele. Survival is poor with most patients dying within a year of diagnosis.

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Grossly these tumors are usually solid but may be at least partially cystic. Microscopically they may exhibit variable patterns of growth, although a tubulopapillary architecture usually predominates. Other histologies include reteform (elongated and compressed tubules), sertoliform (tubular), solid, and biphasic with both epithelial and spindle cell areas. The tumor cells range from cuboidal-to-columnar with eosinophilic-to-basophilic cytoplasm and moderate to marked nuclear atypia.

As previously mentioned rete testis carcinomas are very rare and this diagnosis should be made only after other entities have been excluded. Malignant mesothelioma may have a very similar morphology although it is usually centered along the tunica and is immunoreactive for mesothelial-associated markers such as calretinin and WT-1 rather than those markers associated with adenocarcinoma such as CEA, CD-15 AND B72.3. Testicular Müllerian type tumors may also mimic adenocarcinoma of the rete testis morphologically, but they are more commonly cystic and associated with psammoma bodies. Immunoreactivity for WT-1 and CA-125 is characteristic. Another diagnosis that must be excluded is metastatic carcinoma. Metastases are more commonly bilateral but may occasionally be unilateral. It is usually a manifestation of advanced disease and seen in patients with an established diagnosis of metastatic carcinoma, most commonly from the prostate, lung or gastrointestinal tract.

Tumors of the epididymis are fleetingly rare and will not be discussed, with the exception of clear cell papillary cystadenoma. These lesions may occur sporadically but are usually associated with von Hippel-Lindau disease.^{125,130} Microscopically the lesions exhibit cystic spaces filled with papillary structures lined by cuboidal-to-columnar cells which contain clear cytoplasm, uniform nuclei with occasional inconspicuous nucleoli. Given these morphologic features, it is easy to see why the tumor may be confused with metastatic clear cell carcinoma, particularly of the kidney. A recent study demonstrated that the tumor cells of clear cell papillary cystadenoma are immunoreactive for CK7 but not RCC. Only one of five cases was immunoreactive for CD10. Clear cell renal cell carcinomas should not be immunoreactive for CK7 and CD10 should be positive in a distinct cytoplasmic membranous distribution. At the morphologic level one should remember that clear cell renal cell carcinomas, particularly low grade lesions, will rarely, if ever, have an associated papillary architecture.

Müllerian-Type Epithelial Tumors:

These rare tumors exhibit the full morphologic spectrum seen in their ovarian counterparts; for this reason most authors have used similar nomenclature to describe them.^{125,131-137} Serous and mucinous tumors are most common and the histology may range from a simple cystadenoma to borderline tumor to frank adenocarcinoma. Endometrioid, clear cell and Brenner tumors have also been described as single case reports. The histogenesis of these tumors is a matter of speculation with some authors suggesting Müllerian metaplasia of the tunica vaginalis and others originate from Müllerian rests in the paratesticular soft tissue. Some authors have raised the possibility of these tumors arising from the appendix testis. Interestingly, we have observed striking Müllerian-type metaplasia in this location in a significant number of orchietomy specimens removed for various reasons. Some have even demonstrated a small amount of ovarian-type stroma undermining the Müllerian epithelium.

Müllerian-type serous tumors have been described in children and adults with a peak incidence in the sixth decade of life. They usually present with painful testicular swelling. While borderline lesions are commonly cystic, frankly malignant tumors may be predominantly solid. In the latter cases the tumors invariably are infiltrative and these tumors are capable of local recurrence and metastasis. The morphology of these tumors may exhibit the entire spectrum seen in the ovary. We have observed rare examples of borderline tumors with an associated ovarian-type stroma.

Müllerian-type mucinous tumors are rarer than their serous counterparts. They have a similar age distribution and, once again, exhibit the same morphologic spectrum seen in their ovarian counterparts. Some cases have been described as having an intratesticular rather than a paratesticular location. In these cases extreme care should be taken to rule out the possibility of teratoma primarily, but also metastatic carcinoma. Mucinous cystadenomas and borderline tumors are benign while carcinomas may recur and metastasize.

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Lesions of Mesothelial origin; Hyperplasia, Adenomatoid tumor and Mesothelioma:

Mesothelial hyperplasia occurs as a result of chronic injury as seen in cases of chronic inflammation of adjacent tissues, hydrocele, hematocele, inguinal hernia and underlying tumors, whether benign or malignant.^{125,127,138,139} Microscopically one sees exophytic papillary projections in continuity with the mesothelial lining. Importantly, small tubular structures as well as nests and cords of cells may be present in the superficial submesothelial connective tissue, at times associated with submesothelial fibrosis. Extension into the underlying connective tissue is always superficial with a “horizontal” rather than “vertical” pattern of infiltration. The mesothelial cells will exhibit typical reactive features including binucleation, moderate increase in the nuclear to cytoplasmic ratio, mild hyperchromasia and pleomorphism and minimal mitotic activity. Features characteristic of mesothelioma such as extensive infiltration, solid growth and marked atypia are absent. It has been stated that reactive mesothelium is immunoreactive for Desmin whereas mesothelioma is not. In addition, reactive mesothelial cells are less likely to be immunoreactive for p53. Both will express Calretinin and WT-1. Nevertheless, close examination to the gross and microscopic features of the lesion are likely to lead to the correct diagnosis without the need of immunohistochemistry.

Adenomatoid tumors are a common benign tumor of mesothelial origin.^{125,139-141} Most are asymptomatic and associated with the head of the epididymis, although some may appear to arise within the testis. They may be large; up to 7 cm but are invariably well circumscribed and round-to-oval in shape. The neoplastic cells may be arranged in nests, tubules, cords and even solid sheets or lining small cystic cavities. The cells may be cuboidal, columnar or flattened. The cytoplasm is usually abundant and eosinophilic and may be vacuolated. The associated stroma may be sparse or abundant and can take on a rather fibrous, myoid and even hyalinized appearance. Rarely these tumors may become infarcted in which case they may be associated with severe pain.¹⁴² Microscopically there may be a marked fibroblastic/myofibroblastic proliferation, mimicking a malignant mesenchymal tumor. In these cases the lesion appears to be infiltrative rather than circumscribed. Because of the diverse cytologic and architectural features which may be encountered in adenomatoid tumors, the differential diagnosis is quite extensive. Depending on the case, one may consider metastatic carcinoma (signet ring cells and tubules), liposarcoma (vacuolated cells), yolk sac tumor (vacuolated cells), mesothelioma (infarction with atypical reactive stroma), Sertoli cell tumor (tubules), and Leydig cell tumor (large eosinophilic cells). Taking note of the localization of the lesion, knowledge of the morphologic diversity which may be encountered and prudent use of immunohistochemistry is useful in establishing a correct diagnosis. As expected, these lesions are likely to be immunoreactive for calretinin and WT-1.

Malignant mesotheliomas arise from the tunica vaginalis and are most commonly seen in the sixth and seventh decades of life.^{125,139,143-147} Rare examples have been described in young adults and children. Asbestos exposure has been documented in up to 40% of cases and remains the only established risk factor. A similar relationship with adenomatoid tumor has not been established. Patients usually present with unilateral painful testicular swelling and hydrocele. Gross examination reveals significant thickening of the tunica vaginalis which may also exhibit multiple nodules or masses along its surface. The tunica may be adherent to the underlying testicular tunica albuginea and the tumor mass may extend into the underlying testicular parenchyma. Microscopically the tumor cells have the same features seen in their pleural counterparts, although almost two thirds of cases are pure epithelial with the remaining exhibiting the classic biphasic histology. Rarely will one encounter a pure spindle cell mesothelioma at this site. The tumor cells may take on a complex tubulopapillary architecture superficially, while the invasive component may be composed of tubular structures or solid nest and cords. The tumor cells commonly will exhibit a high nuclear-to-cytoplasmic ratio with moderate-to-marked nuclear atypia and mitotic activity. Necrosis may be present as well as extensive stromal fibrosis. As previously mentioned tumor cells may infiltrate into the testicular hilum and testicular parenchyma, even with intratubular growth. In the former the tumor may mimic a rete testis primary, whereas in the latter the differential diagnosis will include metastatic carcinoma and a germ cell neoplasm such as yolk sac tumor.

Mesotheliomas of the tunica vaginalis have a poor prognosis with almost 50% of patients dying of disease within 2 years of diagnosis. If incompletely excised, they will recur and these inevitably will lead to disease progression and death. Recurrences may be as late as 10 years from diagnosis and for this reason long term clinical follow-up is mandatory.

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The literature describes several mesothelial tumors that are solitary, cytologically banal and well circumscribed under the rubric of “well differentiated mesothelioma”.^{127,148} Others with similar features but cystic have been called “benign cystic mesothelioma”.¹⁴⁹ Great caution must be exercised in making these diagnoses since follow-up have shown the potential for recurrence and progression. While we make a note that mesothelial tumors with these features may be associated with indolent behavior, close clinical follow-up is still warranted. Personally I am very reluctant to make the diagnosis of “benign” mesothelioma.

Metastatic tumors:

As previously discussed, metastatic tumors to the testis, testicular adnexa and paratesticular tissues may mimic primary tumors arising at these sites.^{125,127,150,151} The incidence in resected specimens is low, only because metastases to the gonads usually present in a setting of advanced disease where orchiectomy is unwarranted. Nevertheless orchiectomy containing metastatic disease may be encountered in cases of occult primary, intractable pain or unusual clinical presentation such as unilateral disease.

Of the epithelial tumors, the most common to metastasize to the gonad include prostate, lung, gastrointestinal tract (including appendix, stomach and colon), and kidney, although tumors from virtually any site may be encountered. While not an epithelial tumor, it is important to be aware that metastases from malignant melanoma to the gonad (8%) are not rare.

Desmoplastic Small Round Cell Tumor:

Rare cases of this entity have been described in the scrotum in association with the paratesticular region.^{125,152-154} As in other sites, patients tend to be young and present with a scrotal mass which grossly is tan and firm. Microscopically one encounters the typical “small blue cells” with scant cytoplasm, arranged in tight tubules or solid nests and associated with a dense fibrotic stroma. A tumor-related microvascular proliferation is commonly encountered. Most cases have the typical immunohistochemical profile of cytokeratin, vimentin and desmin positivity with negative staining for S-100 protein, and CD-99. These are aggressive tumors which are likely to have positive regional lymph node or systemic involvement at diagnosis. Despite recent successes with aggressive systemic therapy, prognosis remains poor.¹⁵⁵ The differential diagnosis includes other tumors with “small blue cells” such as lymphoma, rhabdomyosarcoma, and primitive neuroectodermal tumor (PNET). In the rare cases with a tubular architecture, it is conceivable that other tumors such as mesothelioma or sertoli cell tumor may enter in the differential diagnosis.

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Table 1. WHO histological classification of testis tumours*

Germ cell tumours

Intratubular germ cell neoplasia, unclassified

Other types

Tumours of one histological type (pure forms)

Seminoma

 Seminoma with syncytiotrophoblastic cells

Spermatocytic seminoma

 Spermatocytic seminoma with sarcoma

Embryonal carcinoma

Yolk sac tumour

Trophoblastic tumours

 Choriocarcinoma

 Trophoblastic neoplasms other than choriocarcinoma

 Monophasic choriocarcinoma

 Placental site trophoblastic tumour

Teratoma

 Dermoid cyst

 Monodermal teratoma

 Teratoma with somatic type malignancies

Sex cord/gonadal stromal tumours

Pure forms

Leydig cell tumour

Sertoli cell tumour

 Sertoli cell tumour lipid rich variant

 Sclerosing Sertoli cell tumour

 Large cell calcifying Sertolic cell tumour

Granulosa cell tumour

 Adult type granulosa cell tumour

 Juvenile type granulosa cell tumour

Tumours of the thecoma/fibroma group

Sex cord/gonadal stromal tumour

Incompletely differentiated

Sex cord/gonadal stromal tumours, mixed forms

Malignant sex cord/gonadal stromal tumours

Tumours containing both germ cell and sex cord/gonadal stromal elements

 Gonadoblastoma

 Germ cell-sex cord/gonadal stromal tumour, unclassified

* Modified from the World Health Organization Classification of Tumours, Pathology & Genetics: Tumours of the Urinary System and Male Genital Organs, WHO histological classification of testis tumours . Eds. Elbe JN, Sauter G, Epstein JI, Sesterhenn IA. IARC Press, Lyon, France. 2004:218.

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Table 2. Immunohistochemical profile of testicular tumors

Marker	IGCN	Seminoma	Spermatocytic Seminoma	Embryonal Carcinoma	Yolk Sac Tumor	Trophoblastic Tumors +++	Sex- cord gonadal stromal tumors ++
PLAP	+	+	-	+	+/-	-	-
CD-117 (c-kit)	+	+	+/-	-	-	-	-
Oct 3 / 4	+	+	-	+	-	-	-
AFP	-	-	-	-	+	-	-
Cytokeratin +	-	-	-	+	+	+	+/-
Inhibin	-	-	-	-	-	+/-	+
HCG	-	-	-	-	-	+	-

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Table 3. TNM classification of germ cell tumours of the testis *

pTNM pathological classification

- pT – Primary tumour
- pTX Primary tumour cannot be assessed
- pT0 No evidence of primary tumour (e.g. histologic scar in testis)
- pTis Intratubular germ cell neoplasia (carcinoma in situ)
- pT1 Tumour limited to testis and epididymis without vascular/lymphatic invasion, tumour may invade tunica albuginea but not tunica vaginalis
- pT2 Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
- pT3 Tumour invades spermatic cord with or without vascular/lymphatic invasion
- pT4 Tumour invades scrotum with or without vascular/lymphatic invasion

- pN – Regional lymph nodes
- pNX Regional lymph nodes cannot be assessed
- pN0 No regional lymph node metastasis
- pN1 Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension
- pN2 Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension to tumour
- pN3 Metastasis with a lymph node mass more than 5 cm in greatest dimension

* Modified from the World Health Organization Classification of Tumours, Pathology & Genetics: Tumours of the Urinary System and Male Genital Organs, WHO histological classification of testis tumours . Eds. Elbe JN, Sauter G, Epstein JI, Sesterhenn IA. IARC Press, Lyon, France. 2004:219.

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