An Overview of Testicular Germ Cell Tumors

Armita Bahrami, MD; Jae Y. Ro, MD, PhD; Alberto G. Ayala, MD

**Context.**—More than 90% of testicular neoplasms originate from germ cells. Testicular germ cell tumors (GCTs) are a heterogeneous group of neoplasms with diverse histopathology and clinical behavior.

**Objective.**—To help the readers distinguish various subtypes of GCTs, to highlight the clinical manifestations and pathologic features of these tumors, and to review several newly developed immunohistochemical markers for GCTs.

**Data Sources.**—Review of the pertinent literature and our experience.

**Conclusions.**—The etiology of GCTs is largely unknown. Cytopathologic studies suggest a different pathogenesis for each group of infantile/prepubertal GCTs, postpubertal GCTs, and spermatocytic seminoma. Unclassified intratubular germ cell neoplasia is the precursor of all GCTs, excluding spermatocytic seminoma and infantile/prepubertal GCTs. Seminoma, the most common GCT in adults, does not occur before 5 years of age. Spermatocytic seminoma, a tumor of elderly men, typically has an indolent clinical behavior, but rarely it undergoes sarcomatous transformation associated with an aggressive behavior. Embryonal carcinoma is the most common component in mixed GCTs. Eighty percent or more of embryonal carcinoma component and vascular invasion are recognized predictors of occult metastasis for clinical stage I mixed GCTs. Most patients with prepubertal yolk sac tumor, the most common pediatric GCT, have stage I disease at presentation. Most choriocarcinomas present with metastatic symptoms because of the propensity for rapid hematogenous dissemination. Teratomas in children regardless of maturity and dermoid cysts in adults are benign; in contrast, teratomas in adults have a malignant behavior. With appropriate therapy, the majority of testicular GCTs are curable.

(Arch Pathol Lab Med 2007;131:1267–1280)

Testicular tumors are the most common malignancies among American men between the ages of 20 and 39 years. The American Cancer Society has estimated that in the year 2006, 8250 men will develop testicular cancers and 370 men will die of these tumors in the United States. Testis tumors comprise approximately 1% of all cancers in men, but only about 0.1% of cancer deaths in males because the majority of these tumors are curable.

More than 90% of testicular neoplasms originate from germ cells. The incidence of testicular germ cell tumors (GCTs) increases shortly after the onset of puberty and peaks in the fourth decade of life with a median age of 34 years at diagnosis. The incidence varies among different races and various geographic locations. It is 5 times more frequent in white men compared with African American men. Among nations with the highest reported incidence are Scandinavia, Germany, and New Zealand.

Despite several recognized risk factors in the development of GCTs (eg, cryptorchidism or a prior history of GCT), the pathogenesis of germ cell neoplasms including the contributing role of environmental factors or genetic susceptibility remains unknown. Reports from the epidemiologic studies in the United States and Europe have revealed an increase in the incidence of GCTs during the past several decades, but the reason for such a trend is unclear.

Testicular GCTs are a heterogeneous group of neoplasms with diverse histopathology and variable clinical course and prognosis. This diversity is best reflected in various systems offered to classify these tumors. Currently the most comprehensive and widely accepted system of classification is the one proposed by the World Health Organization, which is summarized in Table 1.

<table>
<thead>
<tr>
<th>Type of GCT</th>
<th>Clinical Features</th>
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<tbody>
<tr>
<td>Seminoma</td>
<td>Typically indolent behavior.</td>
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<tr>
<td>Embryonal Carcinoma</td>
<td>Aggressive behavior.</td>
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<tr>
<td>Choriocarcinoma</td>
<td>Rapid hematogenous dissemination.</td>
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<tr>
<td>Teratoma</td>
<td>Malignant behavior.</td>
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There is some evidence that the origin and biology of prepubertal and postpubertal testicular GCTs are distinct from each other. First, the distribution pattern of GCTs in adults and children is different. Testicular neoplasms in adult patients often consist of seminoma, embryonal carcinoma, or mixed testicular GCTs. In the pediatric population, yolk sac tumor and teratoma are the most frequent tumors; on the contrary, seminoma and embryonal carcinoma are rare. Non-GCTs, which account for less than 10% of testicular neoplasms in adults, comprise as high as one third of testis tumors in children. Furthermore, although there is a strong association between postpubertal testicular tumors and intratubular germ cell neoplasia, such association has not been observed in prepubertal GCTs.

Genetic studies have shown that postpubertal testis tumors are often aneuploid with a consistent chromosomal abnormality composed of a gain of short arm of chromosome 12, usually in the form of an isochromosome, i(12p). In contrast tumors arising in prepubertal gonads are typically unassociated with 12p amplification and tend to be diploid. For these reasons, testicular GCTs have been...
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Intratubular germ cell neoplasia, unclassified

- Tumors of 1 histologic type (pure forms)
  - Seminoma
  - Seminoma with syncytiotrophoblastic cells
  - Spermatocytic seminoma
  - Spermatocytic seminoma with sarcoma
  - Embryonal carcinoma
  - Yolk sac tumor
  - Trophoblastic tumors
  - Choriocarcinoma
  - Trophoblastic neoplasms other than choriocarcinoma
  - Monophasic choriocarcinoma
  - Placental site trophoblastic tumor
  - Teratoma
  - Dermoid cyst
  - Monodermal teratoma
  - Teratoma with somatic type malignancies
- Tumors of more than 1 histologic type (mixed forms)
  - Mixed embryonal carcinoma and teratoma
  - Mixed teratoma and seminoma
  - Choriocarcinoma and teratoma/embryonal carcinoma
  - Others

Pathologic Features

Testes with IGCNU are usually normal in size but can be smaller than normal. Histologically, IGCNU is characterized by large primitive atypical cells that are usually twice the size of normal germ cells. These cells lie along the thickened basement membrane of atrophic seminiferous tubules (Figure 1) or may replace the entire tubules. The malignant germ cells have large nuclei with prominent nucleoli and abundant clear cytoplasm that is rich in glycogen, demonstrable by a periodic acid–Schiff (PAS) stain. Because normal germ cells are not stained with PAS, this stain may help to distinguish IGCNU cells from normal cells.

Immunoprofile

Most IGCNU cells stain for placental-like alkaline phosphatase (PLAP)37–40 usually with a membranous and cytoplasmic pattern. Placental-like alkaline phosphatase is an enzyme that in addition to IGCNU is present in embryonal carcinoma, seminoma, and several other GCTs but is usually absent in normal germ cells. The IGCNU cells are also positive for c-Kit (CD117)41,42 and p53 but are negative for cytokeratins, human chorionic gonadotropin (hCG), or α-fetoprotein (AFP). OCT3/4, also known as POU5F1, is a recently recognized marker for GCTs.43 In adult testis, positive immunostaining for OCT3/4 is an indicator for the presence of IGCNU, seminoma, and/or embryonal carcinoma.44 OCT3/4 immunostain highlights IGCNU with a nuclear staining pattern and has proved to be a sensitive and specific marker for detection of IGCNU in biopsy specimens.44,45 D2-40, an antibody raised against a transmembrane mucoprotein called podoplanin, stains IGCNU cells46–48 (Figure 2) as well as lymphatics. Therefore, this antibody can be used to confirm the presence or absence of IGCNU adjacent to invasive GCTs and also to highlight lymphatic invasion.

Clinical Course and Management

Spontaneous regression of IGCNU generally does not occur. Without intervention, about 50% of IGCNU cases will progress to an invasive GCT within 5 years of the diagnosis of IGCNU,31 but on long-term follow-up almost all patients will develop an invasive GCT.49

There is controversy in regard to the management of IGCNU. Orchiectomy clearly provides the highest success rate and perhaps is the therapy of choice in unilateral IGCNU.49,50 Several studies have shown the effectiveness of localized low-dose radiotherapy as compared with chemotherapy in eradication of IGCNU.51,52 Radiation therapy has been considered by some authorities as the treatment of choice in bilateral IGCNU. Although radiotherapy leads to permanent infertility, it has the benefit of preserving hormonal function of the testis. Yet others have advocated surveillance on the basis that if an invasive GCT develops, it will be easy to detect and manage with available effective treatments.

Table 1. 2004 World Health Organization Histologic Classification of Germ Cell Testis Tumors

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<th>Classification</th>
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Figure 1. Intratubular germ cell neoplasia, unclassified, showing large atypical germ cells lying along the basement membrane of atrophic seminiferous tubules (hematoxylin-eosin, original magnification ×400).

Figure 2. Intratubular germ cell neoplasia, unclassified, showing strong immunoreactivity for D2-40 with a membranous pattern in atypical intratubular germ cells (immunoperoxidase, original magnification ×200).

Figure 3. Seminoma with a nested growth pattern separated by lymphocyte-rich fibrovascular trabeculae (hematoxylin-eosin, original magnification ×100).

Figure 4. Seminoma characterized by large uniform evenly dispersed tumor cells displaying clear cytoplasm and distinct cell membrane (hematoxylin-eosin, original magnification ×400).

Figure 5. Tubular variant of seminoma composed of hollow tubular structures lined by characteristic seminoma cells with clear cytoplasm and distinct cytoplasmic border (hematoxylin-eosin, original magnification ×200).

Figure 6. Spermatocytic seminoma characterized by a diffuse proliferation of polymorphous tumor cells, composed of small (lymphocyte-like), intermediate, and large cells with characteristic spireme-type chromatin pattern (hematoxylin-eosin, original magnification ×400).
SEMINOMATOUS GCT

There are 2 types of seminomatous tumors: (1) classic seminoma and its variants and (2) spermatocytic seminoma.

Classic Seminoma and Its Variants

Seminoma is the most common testicular germ cell neoplasm, accounting for approximately 50% of these tumors. In addition, seminoma is a recognizable component in a large proportion of mixed GCTs.

Clinical Features.—The peak incidence is between 34 to 45 years, which is about 1 decade later than that of most other GCTs. Before puberty, seminoma is extremely rare; in fact, it does not occur in the first decade of life especially in children younger than 5 years. Most patients present with a typically painless testicular enlargement. Gynecomastia and infertility are rare presenting symptoms. A fraction of cases may present with symptoms of metastases. Extension to the spermatic cord or epididymis is seen in less than 10% of patients, and in 2% of cases both testes are involved.

Pathologic Features.—Grossly, seminomas are firm when intact, but after sectioning they are soft at palpation with a light tan, moist, homogenous appearance. They may form a single nodule or may be multinodular separated by thick connective tissue septae. Small areas of necrosis or petechial hemorrhage are frequently present, but extensive necrosis, hemorrhage, and cyst formation are uncommon. Gross appearance of seminoma is rather typical and relatively easy to recognize, but similar gross features can be seen in spermatocytic seminoma and testicular lymphoma.

In histologic examination, seminoma cells typically have a solid or nested growth pattern separated by thin fibrovascular trabeculae rich in T-cell lymphocytes (Figure 3). Only 1% of seminomas are devoid of lymphoid infiltration. The individual tumor cells are large, uniform, round to polygonal, and evenly spaced without nuclear overlapping (Figure 4). Seminoma cells display a distinct cell membrane and usually a lightly eosinophilic to clear cytoplasm because of the presence of glycogen, demonstrable by a PAS stain. The nuclei contain 1 or more prominent nucleoli. Mitoses are variable but usually readily identifiable.

Ill-defined granulomatous reactions are frequently seen in seminomas. These reactions at times are so intense that they obscure the seminoma cells. Under these circumstances, the presence of IGCNU in the peritumoral testicular parenchyma is a helpful observation in resolving the diagnostic difficulty. Such reactions, however, more commonly occur in metastatic than in primary locations. In such cases, immunohistochemical staining may contribute to the identification of the nature of lesion.

Histologic Variants of Seminoma.—Seminoma with syncytiotrophoblastic giant cells is a recognized variant of seminoma by the World Health Organization classification system. Syncytiotrophoblasts, which stain positively for hCG and cytokeratin, are seen in approximately 20% of seminomas. The presence of these cells does not impart an adverse prognosis but does correlate with mild elevation of serum hCG, which is generally normalized after orchiectomy. A persistent elevation of serum hCG level following orchiectomy or a high level of serum hCG, in contrast, may indicate a hidden focus of choriocarcinoma.

There are a variety of histologic variants of seminoma characterized by different growth patterns. These histologic profiles, including cribriform/microcystic, tubular, and intertubular may mimic other pathologic entities and create diagnostic confusion. When cribriform/microcystic pattern is the dominant picture, seminoma may superficially resemble yolk sac tumor. The tubular variant (Figure 5) can simulate Sertoli cell tumor. The intertubular variant exhibits a diffuse intertubular growth of seminoma cells similar to the pattern of testicular involvement by hematopoietic neoplasms. Despite these variable growth patterns, seminoma cells retain their cytoplastic features; therefore, the key to the differential diagnosis is attention to cytotologic details of tumors cells. In questionable circumstances, immunohistochemical staining can help to make an accurate diagnosis.

On rare occasions, seminomas may be entirely infarcted and seen as a mass of “ghost” cells suspicious for neoplasm. Florentine et al reported a case of necrotic seminoma in which a Masson trichrome stain plus PLAP immunostain improved the histology and helped to establish the diagnosis. The authors concluded that, in the presence of architectural distortion in a tumor suspicious for seminoma, selected immunostains might aid in arriving at the right diagnosis.

Seminoma with high mitotic rate, also known as anaplastic or atypical seminoma, constitutes 5% to 15% of seminomas. Histologically, it is characterized by increased mitotic activity (3 or more mitoses per 1 high-power field), a greater nuclear pleomorphism, and a paucity of the lymphocytic infiltrate. The prognostic significance of this entity, however, is controversial. Although some studies reported a more aggressive behavior and a lower survival rate in anaplastic seminomas compared with classic seminomas, several other studies failed to demonstrate such differences when the 2 groups were compared stage by stage. One possible explanation is the confounding effect of a higher stage at clinical presentation in anaplastic seminoma compared with classic seminoma.

Immunoprofile.—Immunohistochemically, seminomas are positive for PLAP and c-Kit (CD117) but are negative for epithelial membrane antigen, Ki-1 (CD30), AFP, and hCG. The transcription factor OCT3/4 is a robust diagnostic marker for seminoma as well as for embryonal carcinoma. OCT3/4 has been shown to be a highly sensitive and specific marker for the diagnosis of both tumors in metastatic sites as well. Recent studies have reported that podoplanin, recognized by the commercially available D2-40 monoclonal antibody, is a specific marker for seminoma because unlike OCT3/4, it is not expressed by embryonal carcinoma. Cytokeratin is usually negative but may be focally positive in up to 40% of seminomas.

Treatment of Seminomatous Tumors

Because the management of seminoma and other GCTs following radical inguinal orchiectomy largely depends on the stage of the lesions, before discussion on the management, we shortly review the staging system of testis tumors.

Staging of Testicular Tumors

In 1997, an internationally agreed-on prognostic factor-based staging classification, applicable to both seminoma and nonseminomatous tumors, was published. This well-
Spermatocytic seminoma typically with seminoma is usually assessed radiographically in surgical metastatic disease. Metastatic disease in patients pathologic staging based on the TNM system is largely regional lymph nodes or disseminated disease. Although mass major groups of nonbulky or low-volume (lymph node peritoneal) lymph nodes, which is further divided into 2 stage II is defined by the involvement of regional (retro-tumor is limited to the testis and paratesticular tissues; dehydrogenase reflect tumor turnover.

Specific serum markers including hCG, AFP, and lactate dehydrogenase within normal limits are found in patients with stage I seminoma from 4 large surveillance studies, the primary tumor size (cutoff of 4 cm) and the rete testis invasion achieves a cure rate of more than 90%. Other management options available to patients with stage I seminoma include surveillance and adjuvant chemotherapy. However, with surveillance alone, 15% to 20% of such cases may relapse. In a pooled analysis of 638 patients with stage I seminoma from 4 large surveillance studies, the primary tumor size (cutoff of 4 cm) and the rete testis invasion were 2 important prognostic factors for relapse. A nationwide Danish surveillance study for stage I testicular seminoma similarly showed the tumor size as a significant independent prognostic factor for relapse. In that series, the 4-year survival rates were 94%, 82%, and 64% for tumors measuring less than 3 cm, 3 to 6 cm, and more than 6 cm, respectively. Chemotherapy is the treatment of choice for patients with bulky retroperitoneal involvement and all stage III cases, which results in a complete response rate of approximately 90% in these patients.

Spermatocytic Seminoma

Spermatocytic seminoma is an uncommon germ cell neoplasm that accounts for 1% to 2% of all testis tumors. Spermatocytic seminoma exclusively develops in the testis and has no ovarian or extragonadal counterpart. Classic seminoma and spermatocytic seminoma are believed to have a different pathogenesis and separate cell of origin. The cell origin of spermatocytic seminoma appears to be more differentiated than that of seminoma and capable of spermatogenesis. Cytogenetic studies have shown that spermatocytic seminoma is either diploid or aneuploid with loss of chromosome 9 rather than isochromosome 12p, which is seen in other postpubertal GCTs.

Clinical Features.

Spermatocytic seminoma typically occurs in men older than 50 years of age (median, 55 years), although it may be occasionally seen in younger patients. This tumor classically presents as a painlessly growing testicular mass, usually painless and asymptomatic. The clinical features of spermatocytic seminoma are similar to those of classic seminoma. The tumor typically has a lower incidence of lymph node metastasis compared to classic seminoma. The histologic features of spermatocytic seminoma are characterized by the presence of spermatocytic-like cells with a distinctive histologic appearance.

Table 2. TNM System in Testis Tumors

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Table 3. Stage Grouping of Testis Tumors

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enlarging testicular mass. Although most textbooks have reported the incidence of bilaterality in spermatocytic seminoma to be as high as 10%, compared with only 1.6% in all other GCTs, our personal experience has shown a more or less similar frequency to that of other GCTs including classic seminoma. Spermatocytic seminoma is not associated with cryptorchidism, IGCU, or other germ cell neoplasia; therefore, it is not seen as a component in mixed GCTs.

Spermatocytic seminoma often has an indolent natural history. The risk of metastasis is extremely rare. However, in a small fraction of cases (approximately 6%), the tumor may undergo sarcomatous dedifferentiation, which is associated with an aggressive behavior. Of significance, in cases with sarcomatous dedifferentiation and distant metastasis, the metastases were exclusive to the sarcomatous components.

Pathologic Features.—Grossly, spermatocytic seminomas are well circumscribed, yellow-gray, soft, gelatinous, and sometimes mucoid. The gross appearance may be similar to that of classic seminoma or testicular lymphoma. Foci of cystic change, hemorrhage, and necrosis may be evident. In cases with sarcomatous transformation, the tumor may appear dull gray, fleshy, and more solid.

Histologically, spermatocytic seminoma consists of a diffuse proliferation of polymorphic cells supported by a scanty or edematous stroma. The tumor cells are classically of 3 types (Figure 6): small (lymphocyte-like), intermediate (10–30 μm), and large or giant (50–100 μm), which are usually uninucleated but rarely multinucleated. Intermediate cells are often the predominant cell type and comprise the bulk of the tumor. The nuclei of large and intermediate cells often display a typical spiral deposition of chromatin similar to that seen in spermatocytes. The nuclei of small cells are rather dense. The cytoplasm of tumor cells is eosinophilic to amphophilic and does not contain glycogen. A high mitotic activity is often appreciated. Intratubular spread of spermatocytic seminoma in the adjacent seminiferous tubules may be present.

The sarcomatous component of spermatocytic seminoma is usually composed of undifferentiated spindle cells, but differentiated patterns such as rhabdomyosarcoma and chondrosarcoma have also been reported. An “anaplastic” variant of spermatocytic seminoma, characterized by a predominance of anaplastic cells with prominent nucleoli, extensive necrosis, and vascular or tunical invasion without sarcomatous elements, has been described in a small series. In all cases, foci of classical spermatocytic seminoma within the tumor were present. Although the clinical course of patients in that series was indolent and essentially similar to that of typical spermatocytic seminoma, the prognostic significance of this variant needs to be determined in larger series with long-term follow-up.

Immunoprofile.—Many of the markers including OCT3/4 and PLAP, which are demonstrated in other types of GCTs, have not been detected in spermatocytic seminoma. Spermatocytic seminoma cells do not react with hCG, AFP, leukocyte common antigen, or CD30. However, consistent expression of c-Kit and germ cell marker VASA as well as focal cytoplasmic staining for CAM 5.2 in some cases have been described.

Differential Diagnosis.—The differential diagnoses of spermatocytic seminoma mainly include classic seminoma and malignant lymphoma. The presence of lymphocyte-rich fibrovascular trabeculae, granulomas, and the uniformity of a single-cell population distinguish classic seminoma from spermatocytic seminoma. Large cell lymphoma, the most common testicular malignancy in the same age group, is characterized by an interstitial growth pattern. Cytologically, lymphoma cells display a fine nuclear chromatin pattern as compared with the typical spireme-like chromatin distribution of spermatocytic seminoma. In difficult cases, immunohistochemical staining for lymphoid markers can aid to differentiate the 2 entities.

Clinical Course and Management.—The prognosis of spermatocytic seminoma is remarkably good with a very low tendency for metastasis. Although low-dose radiation to the abdomen following orchiectomy has been traditionally the treatment of choice, surveillance is currently becoming the preferred management option by most authorities. Spematocytic seminoma with sarcomatous transformation necessitates aggressive treatment with chemotherapy although the prognosis remains very poor despite chemotherapy.

NONSEMINOMATOUS GCT

Nonseminomatous GCTs are composed of embryonal carcinoma, yolk sac tumor, immature or mature teratoma, choriocarcinoma, and other rare trophoblastic tumors. These tumor types are often seen together in various combinations, referred to as mixed GCTs, which may also include seminoma. The words nonseminomatous and mixed GCTs are usually used interchangeably in daily clinical practice.

Embyronal Carcinoma

Pure embryonal carcinoma, although relatively uncommon, is the second most common single-cell-type GCT after seminoma. Embryonal carcinoma as a component, however, is present in more than 80% of mixed GCTs.

Clinical Features.—Pure embryonal carcinoma occurs most frequently between 25 and 35 years of age, which is 10 years earlier than the age range for seminoma. Embryonal carcinoma is rare after the age of 50 years and does not occur in infancy. Most patients present with a painless unilateral enlarging testicular mass. Approximately two thirds of cases have retroperitoneal lymph node or distant metastases at the time of diagnosis.

Pathologic Features.—Grossly, embryonal carcinoma often presents as a poorly demarcated mass with a soft gray-tan cut surface, frequently associated with large foci of hemorrhage and necrosis. Extension into the cord and epididymis is not uncommon.

On microscopic examination, embryonal carcinoma displays variable growth patterns, including solid, syncytial, acinar, tubular, or papillary arrangement. The neoplastic cells are polygonal, undifferentiated, and epithelial looking with large vesicular and empty-looking nuclei and thick, distinct nuclear membrane. The cytoplasm is usually abundant and finely granular with a nondistinct cell border. Intratubular germ cell neoplasia, unclassified, and less commonly intratubular embryonal carcinoma may be seen in the adjacent testicular parenchyma. Vascular/lymphatic invasion in the peritumoral tissue is an important feature to document. True vascular/lymphatic invasion, however, should be distinguished from the artifactual in-
travascular implants, which easily happen during tissue sectioning because of the cellular and friable nature of the tumor.

**Immunoprofile.**—Embryonal carcinomas are commonly positive for cytokeratin but negative for epithelial membrane antigen, which can help distinguish a metastatic embryonal carcinoma from a somatic carcinoma. Placental-like alkaline phosphatase and OCT3/4 are both sensitive markers for embryonal carcinoma but do not discriminate against seminoma. D2-40, which stains seminoma, in contrast, does not label embryonal carcinoma. Ki-1 (CD30), which is also a sensitive marker for embryonal carcinoma (Figure 8), stains no other GCTs including seminoma or yolk sac tumor. CD30 expression, however, is frequently lost in metastatic embryonal carcinoma after chemotherapy. The embryonal carcinoma cells are usually negative for carcinoembryonic antigen, hCG, and CD117 (c-Kit). When distinction of seminoma from the solid pattern of embryonal carcinoma is a diagnostic consideration, a cytokeratin cocktail, CD30, D2-40, and CD117 immunostaining used in combination may help the differential diagnosis. Although AFP may occasionally stain scattered tumor cells, the presence of AFP, either immunohistochemically or in the serum, is generally regarded as an evidence of yolk sac differentiation.

**Yolk Sac Tumor**

Yolk sac tumor is a germ cell neoplasm that differentiates in the direction of the embryonic yolk sac, allantois, and extraembryonic mesenchyme. It is the most common testicular neoplasm in the pediatric population, accounting for approximately half of the prepubertal testis tumors. Childhood yolk sac tumor does not appear to be associated with cryptorchidism or IGCNU. Yolk sac tumor in children is almost always seen in the pure form. On the contrary, in adults it is seen only admixed with other neoplastic germ cell elements, and the pure form is extremely rare. Foci of yolk sac tumor are found in 40% of mixed GCTs in adults.

**Clinical Features.**—In children, the median age at presentation is 16 months (range, newborn to 11 years). Patients usually present with a rapid painless testicular enlargement. About 80% of pediatric yolk sac tumor present with stage I disease.

Elevated serum AFP, which is seen in 95% to 100% of patients with testis tumors containing yolk sac elements, is a useful indicator for the presence of this tumor. In addition, serial measurement of serum AFP provides a mean for monitoring therapy and for early detection of metastases and recurrences. However, caution should be exercised in interpretation of AFP values in children younger than 6 months in whom serum AFP may be physiologically elevated.

**Pathologic Features.**—On gross examination, yolk sac tumor presents as a solid, lobulated, gray-white, soft ill-defined mass with a gelatinous to mucinous cut surface. Hemorrhage, necrosis, and cystic change may be present.

Microscopically, the key to the recognition of yolk sac tumor is the presence of a spectrum of histologic patterns, including reticular (microcystic, vacuolated, honeycomb), macrocystic, endodermal sinus (perivascular, festoon), papillary, solid, glandular-alveolar, myxoid, sarcomatoid (spindle cell), hepatoid, and parietal patterns. Several of these histologic appearances are usually admixed in a tumor. The reticular-microcystic pattern is the most common feature, occurring in 80% of patients (Figure 9, A). The anastomosing thin cords and irregular loose spaces are lined by deceptively benign-appearing flat or cuboidal tumor cells. The cytoplasmic vacuoles within the tumor cells form a meshwork of vacuolated lipoblast-like cells imparting a honeycomb appearance.

The most distinctive histologic feature is the one forming Schiller-Duval bodies in which a central fibrovascular core is surrounded by malignant cuboidal to columnar cells (Figure 9, B). Another helpful histologic finding is the presence of round, homogeneous diastase-resistant PAS-positive hyaline globules (Figure 10), which contain AFP or α1-antitrypsin. These globules are seen in 85% of cases and represent visceral yolk sac differentiation. Parietal yolk sac differentiation in contrast is characterized by
the presence of irregular thick eosinophilic basement membrane deposits that are PAS positive but usually negative with AFP.

Rarely, yolk sac tumors may be entirely composed of 1 single histologic pattern. These histologic variants at times may cause diagnostic challenges; for example, a solid yolk sac tumor can be confused with seminoma or embryonal carcinoma. Immunohistochemical staining in such cases can help to make an accurate diagnosis.

**Immunoprofile.—**Most yolk sac tumors are positive for AFP, but staining is variable and often patchy. Therefore, a negative staining for AFP does not completely exclude a diagnosis of yolk sac tumor. In addition in rare circumstances, a viable yolk sac tumor in the metastatic site may lose its staining for AFP even though the primary tumor is positive for it. Staining for cytokeratin, in contrast, is usually diffuse and intensely positive. Yolk sac tumors are often positive for PLAP and α1-antitrypsin but negative for Ki-1, hCG, and OCT3/4. In a recent report, Glypican 3, a membrane-bound heparin sulfate proteoglycan, has been found to be a very sensitive and relatively specific marker for yolk sac tumor and choriocarcinoma against seminoma, embryonal carcinoma, and teratoma.

**Treatment.**—For stage I pediatric patients, the management includes orchectomy followed by close observation. Metastatic yolk sac tumor or recurrence should be treated with adjuvant chemotherapy. In children with yolk sac tumor, there is evidence of a predilection for hematogenous spread without lymph node involvement. Because only a minority of metastatic prepubertal yolk sac tumors have metastases limited to the retroperitoneum, retroperitoneal lymph node dissection is usually reserved for patients with recurrent retroperitoneal masses following chemotherapy. Overall, the survival of children with yolk sac tumor is excellent. Treatment in adult cases, which is similar to that of other nonseminomatous GCTs, is discussed in the management section.

**Choriocarcinoma**

Pure choriocarcinoma is extremely rare and accounts for less than 1% of testicular tumors. However as a component, choriocarcinoma is seen in approximately 8% of mixed GCTs.

**Clinical Features.**—Patients with choriocarcinoma are typically in the second or third decades of life. Most cases present with metastatic symptoms, including hemoptysis, gastrointestinal bleeding, or neurologic symptoms rather than a testicular mass. The testis itself usually appears normal or even small because of the regression of the primary site, although depending on the extent of hemorrhage, sometimes it may appear enlarged.

Choriocarcinoma is associated with very high values of hCG (>100,000 mIU/mL). Because of cross-reactivity of hCG with luteinizing and thyroid-stimulating hormones, some patients may present with symptoms related to endocrine abnormalities, including gynecomastia and hyperthyroidism, respectively.

**Pathologic Features.**—On gross examination, choriocarcinoma appears as a hemorrhagic nodule, which is often surrounded by a rim of gray-white tissue at the periphery. Occasionally, the tumor is totally burnt out and only a fibrous scar is discernible. Microscopically, choriocarcinoma is composed of an admixture of 2 cell components, syncytiotrophoblasts and cytotrophoblasts. The individual syncytiotrophoblasts are multinucleated with dark eosinophilic cytoplasm and multiple irregular large hyperchromatic nuclei. The cytotrophoblasts are uniform, medium-sized polygonal cells with abundant cytoplasm, single nuclei, and distinct cytoplasmic border. These cells are usually randomly arranged in solid nests or sheets within a background of hemorrhagic necrosis. In more differentiated areas, syncytiotrophoblasts classically wrap clusters of cytotrophoblasts in a villouslike arrangement (Figure 11).

Monophasic choriocarcinoma is a variant of choriocarcinoma with a monomorphic appearance mainly composed of cytotrophoblasts with inconspicuous syncytiotrophoblastic cells. Because cytotrophoblasts without combination with syncytiotrophoblasts are histologically nondescript, a monophasic choriocarcinoma may resemble seminoma, embryonal carcinoma, or the solid variant of yolk sac tumor.

The testicular counterpart of placental site trophoblastic tumor has been described in only a few cases. These tumors were predominantly composed of a proliferation of intermediate trophoblast. The neoplastic cells showed diffuse immunoreactivity for human placental lactogen and patchy staining for hCG.

Cystic trophoblastic tumors are uncommon lesions described in retroperitoneal resections after chemotherapy in patients with GCTs. These lesions consist of circumscribed small cysts lined by a predominance of mononucleated trophoblastic cells with smudged nuclei and infrequent mitotic figures. These lesions appear to have little aggressive potential, and their presence in postchemotherapy resections does not warrant additional treatment.

Of note, scattered syncytiotrophoblasts, which may be seen in about 20% of pure seminomas, should not be misinterpreted as foci of choriocarcinoma.
Figure 10. Characteristic round, homogeneous eosinophilic hyaline globules (arrow) in a reticular background of yolk sac tumor (hematoxylin-eosin, original magnification ×200).

Figure 11. Choriocarcinoma showing an admixture of syncytiotrophoblasts with multiple nuclei and eosinophilic cytoplasm (long arrow) wrapping around a cluster of cytotrophoblasts (short arrow) (hematoxylin-eosin, original magnification ×200).

Figure 12. Immature teratoma composed of an epithelial component surrounded by immature cellular spindle cell stroma (hematoxylin-eosin, original magnification ×200).

Seminoma with choriocarcinoma is extremely rare in our experience. In addition, we have not seen cases of seminoma with choriocarcinoma without other GCT components.

Immunoprofile.—Immunostaining for hCG is constantly positive in syncytiotrophoblasts and also in transitional cells between syncytiotrophoblasts and cytotrophoblasts (intermediate trophoblasts), but it is usually negative in cytotrophoblasts. Inhibin\(^29\) stains cytotrophoblasts and intermediate trophoblasts. Intermediate trophoblasts, if present, may also stain for human placental lactogen and human leukocyte antigen G, a nonclassical MHC class I antigen.\(^130\) Cytokeratin is positive in all of the cell types.\(^131\) Vimentin is negative, but carcinomaembryonic antigen may be positive in syncytiotrophoblasts.\(^132\) The PLAP immunostain is positive in 50% of choriocarcinomas.\(^59\) Glypican 3 has been recently demonstrated to be expressed in choriocarcinoma, with stronger immunoreactivity in syncytiotrophoblasts compared with cytotrophoblasts.\(^133\)

Prognosis.—Because of its predilection for rapid hematogenous dissemination, choriocarcinoma has a worse prognosis than other types of GCT.\(^134\) In fact, the prognosis of a pure choriocarcinoma is worse than a “mixed GCT with choriocarcinomatous component.”\(^14\) There is a high incidence of brain metastasis because of the propensity for angioinvasion.\(^134\) Choriocarcinoma also commonly involves the retroperitoneal lymph nodes. Both higher values of hCG and greater proportion of choriocarcinoma elements in a GCT are indicative of a more adverse outcome. The management does not differ from the management of any other histologic types of nonseminomatous GCT.

Teratoma

Teratomas are tumors composed of variable types of tissue representing 1 or more of the germinal layers of endoderm, mesoderm, and ectoderm. A tumor composed of only 1 of the 3 germ layers is defined as monodermal teratoma. Mature teratomas are composed of entirely mature well-differentiated components. In contrast, immature teratomas contain embryonic or fetallike tissues, which are typically accompanied by mature elements.

Teratoma occurs in both children and adults, but the biologic behavior of the tumor is substantially different between the 2 groups. In adults, teratoma as a pure neoplasm is uncommon (only 2%-3% of all GCTs); however, as a component, it is present in almost 50% of mixed GCTs.\(^135\) In contrast in children, almost all teratomas are pure neoplasms. Teratoma is the second most common prepubertal testicular neoplasm after yolk sac tumor, accounting for 14% of these tumors.\(^19\) Most prepubertal teratomas are exclusively composed of mature tissues; nevertheless, all of them behave in a benign manner regardless of the mature or immature nature of their components.\(^19\) On the other hand, most postpubertal teratomas are immature, although even purely mature teratomas in adults are at risk of metastases. In other words, the immaturity of teratomatous components is not an indicator of poor biologic behavior in the primary tumor; rather, the age of the patient is important. Most teratomas in children are diploid and lack amplification of short arm of chromosome 12; in contrast, teratomas in postpubertal patients are aneuploid and have isochromosome 12p.\(^136\)

Clinical Features.—Most prepubertal teratomas are seen in children younger than 4 years with a mean age of 20 months.\(^137\) Children typically present with a testicular mass detected by the parents. Most postpubertal cases are young adults presenting with testicular swelling or sometimes with symptoms associated with metastasis. In a series from Indiana, nearly 37% of adult patients with pure teratoma presented with advanced disease.\(^138\)

Pathologic Features.—On gross examination, teratomas
are usually well-circumscribed, solid, firm, nodular or multicystic tumors. Their cut surface is heterogeneous as an expression of variable tissue types. Cysts may be filled with clear serous fluid, pearly gelatinous, or mucinous material. Cartilage or bony spicules may be grossly discernible. Other grossly recognizable tissues including sebaceous material, hair, and teeth, unlike ovarian teratoma, are not common findings in a testicular teratoma.

In microscopic examination, variable ectodermal, endodermal, and mesodermal tissues admixed in either a disorganized or an organized arrangement are seen. Pure mature teratomas are composed of tissue components resembling adult somatic tissues. The most common components are different types of epithelium, neural tissue, glandular tissue, and cartilage, although virtually any other mature somatic components may be present. Significant cytologic atypia is frequently seen in mature elements of postpubertal teratomas, signifying the aneuploid nature of teratomas in adults.

Immaturity in a teratoma is defined as tissues that cannot be recognized as adult tissue elements (Figure 12) or those that resemble embryonic or fetal tissue. Most immature teratomatous elements of GCTs are cellular spindle mesenchymal components, but immature neural and epithelial elements are also seen. The spindle cells show frequent mitoses.

The vascular invasive component of postpubertal testicular teratoma may include either the teratomatous elements or the precursor cells that have the capacity to differentiate into various cell lines. Therefore, the cellular components of metastatic sites may differ from those of their primary tumor counterpart.

Orchiectomy is curative in pure teratomas in prepubertal patients. The treatment in adults is discussed later with other nonseminomatous GCTs.

### Dermoid Cyst

It is controversial whether the rare dermoid cyst of the testis should be classified as a specialized form of mature teratoma or separately. Dermoid cysts characteristically contain cysts lined by keratinizing squamous epithelium associated with skin appendages; however, noncutaneous mature teratomatous elements may also exist in a dermoid cyst. In contrast to postpubertal teratoma, dermoid cyst is not associated with IGCNU and also does not have any malignant potential. Because teratomas in adults and dermoid cysts are prognostically different, it is important to extensively sample the lesion as well as the uninvolved testicular parenchyma to exclude any immature teratomatous components or IGCNU in the adjacent testis before rendering the diagnosis of dermoid cyst.

### Mixed GCTs

Mixed GCTs of the testis are the second most common GCTs in adults (following seminoma), comprising 30% to 50% of the cases. Tumors that contain seminoma occur at a later age than those without a seminomatous component. Mixed GCTs are rarely seen in prepubertal gonads. Serum elevation of AFP and hCG are common, correlating with the presence of yolk sac tumor elements and syncytiotrophoblastic cells (either singly or as part of choriocarcinoma), respectively.

Grossly, mixed GCTs have a variegated cut surface, reflecting their various tissue components. The most common histologic subtypes in a mixed GCT in order of frequency are embryonal carcinoma, teratoma, yolk sac tumor, seminoma, and choriocarcinoma. The histologic appearance of various types of GCTs is identical to that of their pure form. These components are present in variable proportions and in most cases are distributed haphazardly throughout the tumor. Yolk sac tumor is the most frequently overlooked component in a mixed GCT. Of all possible histologic combinations, some of the commonly observed forms include embryonal carcinoma/teratoma and embryonal carcinoma/semimina, reflecting the high frequency of embryonal carcinoma in mixed GCTs. In classifying more than 6000 testis tumors, Mostofi found that in about 60% of cases, more than 1 histologic elements was present, and the most frequent combination was embryonal carcinoma, yolk sac tumor, teratoma, and syncytiotrophoblasts. Yet in another series, embryonal carcinoma/teratoma was the most commonly observed combination.

For mixed GCTs, all components present in the tumor should be listed in the pathology report along with the approximate proportion of each component, in particular that of embryonal carcinoma. The significance of embryonal carcinoma proportion in a mixed GCT is discussed in the section on management of nonseminomatous GCTs.

### Polyembryoma and Diffuse Embryoma

Polyembryoma and diffuse embryoma are 2 distinct forms of mixed GCTs. Polyembryoma consists of a mixture of embryonal carcinoma and yolk sac tumor with an associated amnion-like cavity, forming embryoid bodies (Figure 13, A) dispersed in a myxoid stoma. In diffuse embryoma, there is an intermingling of embryonal carcinoma and yolk sac tumor of approximately equal amount (Figure 13, B) arranged diffusely in a necklace-like pattern, in which a single layer of yolk sac tumor covers the embryonal carcinoma as a collar.
Treatment of Nonseminomatous Tumors

The treatment for nonseminomatous or mixed GCT largely depends on whether the tumor is localized to the testis or has already metastasized to the retroperitoneal lymph nodes or other sites. Most nonseminomatous GCTs including the pure variants initially metastasize to the retroperitoneum; however, embryonal carcinoma and choriocarcinoma may concomitantly metastasize via vascular invasion and go to distant sites early in the course of disease.142 Initial clinical and radiographic examination (clinical staging) provides clues to the best management of patients with nonseminomatous GCTs.

Because of the high likelihood of retroperitoneal lymph node involvement in patients with nonseminomatous GCTs, the standard management for a localized disease (stage I) is nerve-sparing retroperitoneal lymph node dissection. One of the advantages of this management is to have a true staging procedure that provides a mean for discovery of microscopic retroperitoneal metastasis. Moreover, the procedure alone is curative in a high percentage of cases. Because in the past, retroperitoneal node dissections rendered a high percentage of patients sterile (dry ejaculation), current surgery attempts to preserve the sympathetic and parasympathetic ganglia.

Another management option for localized disease is surveillance. Because some patients may relapse even 1 year after orchietomy, surveillance requires at least 2 years of follow-up; therefore, it is long and expensive, necessitating monthly chest x-rays, computed tomography/magnetic resonance imaging of the abdomen every 3 months, and monthly determination of serum markers. Thus, not all patients are good candidates for surveillance; for example, patients with psychiatric problems or drug addicts are not selected for this treatment approach. Many other patients by choice may not elect such prolonged monitoring either. In addition, patients with high risk of occult retroperitoneal metastasis should be excluded from surveillance management. For example, patients with pure embryonal carcinoma are not good candidates because a high percentage may have microscopic metastatic disease. Several studies have shown that the presence of embryonal carcinoma in excess of 80% in the primary tumor and vascular invasion are independent predictors for metastatic disease in patients with clinical stage I mixed GCTs.143–146 The presence of these factors indicates a high-risk group that would be best to exclude from surveillance therapy. Overall, the cure rate for patients with nonseminomatous GCTs in clinical stage I exceeds 95%.9

The management for metastatic disease to the retroperitoneum (stage II disease) is either retroperitoneal lymph node dissection or chemotherapy. Persistent elevation of serum markers after orchietomy is usually indicative of metastatic disease. With low-volume disease (nonbulky stage II), both treatments render similar results. As an exception, patients with a prominent teratoma component in the primary usually undergo retroperitoneal lymph node dissection instead of chemotherapy. If these patients are initially treated with chemotherapy, the teratoma component in the retroperitoneum may not respond and continues to grow (growing teratoma syndrome).

Initial chemotherapy is indicated for both bulky stage II and stage III disease, which may be followed by post-chemotherapy surgery to eradicate any form of residual disease if present. One clinically important pathologic finding in the evaluation of postchemotherapy residual tissue is the presence of embryonal carcinoma component, which requires implementation of additional chemotherapy.142 Existing teratoma, in contrast, does not impose additional therapy, although the presence of neuroectodermal components in a metastatic site imparts a poor prognosis. Combination chemotherapy has resulted in complete remission in 70% to 80% of patients with distant metastasis.147

SOMATIC MALIGNANCIES ARISING IN TESTICULAR GCT

Most somatic malignancies arising in testicular GCTs originate from teratomatous component of a mixed GCT, but occasionally they may derive from yolk sac tumor.148,149 Some sarcomas, as described before, may also develop from dedifferentiation of spermatocytic seminoma.96–101

The somatic malignancies arising in GCTs include various types of sarcomas, including undifferentiated spindle cell tumors or differentiated forms (eg, rhabdomyosarcoma or leiomyosarcoma), primitive neuroectodermal tumor, and carcinomas.148–151 Somatic malignancies can arise in the primary GCT or in the metastatic sites. Somatic tumors confined to the testis generally do not affect the prognosis of GCT; in contrast, those developing in the extratesticular sites, especially primitive neuroectodermal tumor and rhabdomyosarcoma, are likely associated with a poor prognosis.150–152

Recognition of somatic malignancy from primitive type tissues within teratomas at times can be difficult. Malignancy of mesenchymal elements is characterized by an expansile growth of a pure mesenchymal component (stromal overgrowth), that is, a microscopic field in excess of that viewed with a ×4 objective.153 This criterion is adapted from the definition of stromal overgrowth in malignant transformation of phyllodes tumor of the breast. The presence of stromal invasion, on the other hand, is a useful criterion for defining malignancy of epithelial elements.

Most somatic tumors arising in GCTs have manifested following chemotherapy. Approximately 3% to 6% of patients with metastatic GCTs treated with chemotherapy have shown malignant transformation.148,151 It should be noted that chemotherapy by itself is not a prerequisite for the development of these tumors. Rather, it is the destruction of chemosensitive GCTs that allows the pre-existing somatic malignancies, which are nonresponsive to chemotherapy, to manifest after chemotherapy.148 Surgical resection is the treatment of choice in these tumors.

CONCLUSION

Because decision on the mode of therapy largely relies on pathologic classification of GCTs, pathology reports should include factors that are prognostically significant or have implications for therapeutic decision. The increased interest in surveillance-only management of non–high-risk patients with stage I disease necessitates accurate identification of high-risk patients in whom surveillance is not recommended. Vascular invasion and the proportion of embryonal carcinoma component in a mixed GCT, which are both reliable prognosticators for identification of high-risk patients, can be best evaluated through careful examination of an appropriately sampled testicular neoplasm. The differences in management between seminoma and nonseminoma tumors as well as the potential for only focal existence of nonseminomatous components
necessitate adequate sampling of testis tumors for microscopic examination before a diagnosis of seminoma is made (in general, 1 section per 1-cm tumor diameter, including areas with differing appearances). An elevated serum AFP level virtually excludes a diagnosis of pure seminoma, even though microscopic evaluation does not appreciate the nonseminomatous germ cell elements. Although based on a small study, minor elevations of serum AFP (<16 ng/mL) may not be necessarily indicative of the presence of a yolk sac component.154

To help the clinician select the best treatment for individual patients, the following information should be provided in the pathology report of a testicular GCT: (1) gross features such as tumor size, tumor necrosis, or hemorrhage; (2) local extension, including invasion into the spermatic cord or scrotum, and the status of spermatic cord margin; (3) tumor classification group: seminoma versus nonseminoma (pure or mixed forms); (4) for mixed GCT, a list of various histologic components in the tumor with the approximate percentage of each component; (5) presence or absence of vascular or lymphatic invasion; and (6) the presence of a yolk sac component.154

Several stainings may be useful to help the pathologist in establishing the diagnosis of GCT. Pathologists, therefore, should be fully aware of histologic variants of these diverse tumors.

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