Germ Cell Tumors of the Testis
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Testicular tumors are relatively uncommon neoplasms, and most are cured, so the death rate from testicular cancer is low. It is estimated that there will be 8,820 new cases of testicular cancer in 2015 and 380 deaths. (1) Testicular cancer is compared with some other forms of male genitourinary cancer in the following table:

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>220,800</td>
</tr>
<tr>
<td>Bladder</td>
<td>56,320</td>
</tr>
<tr>
<td>Kidney</td>
<td>38,270</td>
</tr>
<tr>
<td>Testis</td>
<td>8430</td>
</tr>
</tbody>
</table>

A few years ago I spoke on sex cord-stromal tumors of the testis here at our Current Issues Course. This year, I will focus on germ cell tumors, which are by far the most common form of testicular cancer; they account for more than 95% of testicular tumors. Testicular germ cell tumors have much in common with germ cell tumors of the ovary, but they are much more frequent. In addition to gross pathology and routine light microscopy, pathologists tend to rely heavily on immunohistochemistry to diagnose testicular germ cell tumors. A nice review of the use of immunohistochemistry for this purpose was recently published. (2)

Intratubular Germ Cell Neoplasia, Unclassified (IGCNU)

IGCNU is thought to be the precursor of most forms of invasive germ cell tumors. (3) The seminiferous tubules adjacent to invasive germ cell tumors contain IGCNU in more than 90% of cases. This condition is also called testicular carcinoma in situ, especially in Europe, (4) but since not all germ cell tumors have an epithelial phenotype (seminoma, for example), the name IGCNU is preferred in the US. IGCNU is not seen adjacent to pediatric germ cell tumors such as the infantile forms of yolk sac tumor and teratoma nor is it seen adjacent to dermoid cysts or spermatocytic seminomas. IGCNU cells are aneuploid but unlike most invasive germ cell tumors, IGCNU lacks an i12p or 12p amplification.

Clinical studies of patients with IGCNU reveal a high rate of progression to invasive germ cell tumors. 50% develop an invasive germ cell tumor by 5 years and 70% by 7 years. It is assumed that all patients with IGCNU will eventually develop invasive germ cell tumors. The genetic basis of IGCNU is thought to be established in primordial germ cells during fetal life. It remains dormant until puberty, when it evolves and eventually progresses to an invasive neoplasm, typically in young men. IGCNU is detected with the greatest frequency in high risk patients. It is found in 2 to 8% of cryptorchid patients, in 5% of contralateral testes of men with a germ cell tumor, and at even higher rates in patients with gonadal dysgenesis or the androgen insensitivity syndrome. IGCNU is found in less than 1% of the normal population. Testicular biopsy, which is performed in postpubertal patients, is a very sensitive method of diagnosis. Generally, if the testis is atrophic or fibrotic posterior biopsies near the rete testis are most successful. Since IGCNU can be bilateral both testes need to be biopsied.
Pathology

IGCNU is a microscopic finding, and there is no specific gross abnormality in the testis. Microscopically, IGCNU is characterized by malignant germ cells growing along the basal layer of the seminiferous tubules. The abnormal cells are not homogeneously distributed and they vary in number from case to case. They are large cells with clear cytoplasm, larger nuclei than spermatogonia and one or more prominent nucleoli. The nuclear membranes are thick and irregular. Glycogen can usually be demonstrated in the cytoplasm with the PAS stain. IGCNU cells resemble seminoma cells. They are typically present in abnormal tubules that are decreased in diameter and have a thickened eosinophilic hyalinized basement membrane. There is decreased or absent normal spermatogenesis but Sertoli cells persist and are intermixed with the IGCNU cells. In IGCNU the atypical cells sometimes extend into the ductal system, with pagetoid spread into the rete testis and even into the epididymis or vas.

While IGCNU can be identified in routine H&E stained slides, I like to confirm the diagnosis with immunohistochemical stains. The abnormal cells show staining with seminoma markers, so there is strong nuclear staining for OCT4, SALL4 and NANOG, and there is cytoplasmic/membrane staining for PLAP, CD117 and D2-40. I usually use a combination of OCT4 and D2-40, although OCT4 alone has been shown to be effective in screening testicular biopsies for IGCNU; it sometimes identifies cases that are not picked up on routine H&E sections. (5) Issues with some of these stains include limited staining for CD117 in spermatogonia and nonspecific staining for SALL4 in nonneoplastic germ cells. These markers have to be used with caution in young children because staining persists from fetal life up to about age 18 months, and staining in very young patients could thus mark normal germ cells, not tumor cells.

Treatment is by orchiectomy if the IGCNU is unilateral and low dose radiation if it is bilateral. The low dose irradiation eradicates both IGCNU and normal germ cells, which prevents development of an invasive germ cell tumor but causes sterility. Leydig cells are preserved, so there is no hormonal deficit.

In addition to IGCNU, more extensive intratubular germ cell proliferations can be present, and the most common types can be classified as intratubular seminoma and intratubular embryonal carcinoma. Intratubular embryonal carcinoma can show comedonecrosis and can contain large coarse calcifications.

Staging of Germ Cell Tumors

The staging of testicular cancer is complicated, and depends on the characteristics of the primary tumor, the presence and size of lymph node metastases, serum tumor markers, and the presence of distant metastases. In practice, clinical stage I is important to recognize, because it has the most treatment options. Stage I is determined based on pathologic examination of the testicular tumor (pT1-pT4), radiographic evaluation of the pelvis, abdomen and chest to determine the N and M categories, and serologic evaluation to detect tumor markers, which determine the S category. A tumor with any pT can be stage I as long as there is no evidence of lymph node or distant metastasis. For proper staging, the tumor and surrounding testis should be extensively sampled for histologic examination, documenting all grossly different parts of the tumor, the relationship of the tumor to the tunica albuginea and the tunica vaginalis, the hilum, epididymis and spermatic cord, and the periphery of the tumor with surrounding residual testis. In addition, a section of testis remote from the tumor should be taken.

<table>
<thead>
<tr>
<th>pT1</th>
<th>Limited to testis and epididymis without lymphovascular invasion; may invade into tunica albuginea but not the tunica vaginalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2</td>
<td>Limited to testis and epididymis, with lymphovascular invasion or invasion through the tunica albuginea with involvement of the tunica vaginalis</td>
</tr>
<tr>
<td>pT3</td>
<td>Invasion of the spermatic cord with or without lymphovascular invasion</td>
</tr>
</tbody>
</table>

2
**Seminoma**

Seminoma is the most common germ cell tumor, occurring in pure form and as a component of a mixed germ cell tumor. It reportedly accounts for up to 50% of pure tumors. In a report from one large medical center in the US, 136 malignant germ cell tumors were identified, of which 56 were pure seminomas (40%), 50 were nonseminomatous germ cell tumors (35%), and 35 were mixed germ cell tumors that had a seminoma component (25%). (6) The average patient age is 40.5 years, which is about 10 years older than the average for patients with nonseminomatous germ cell tumors. Seminoma basically never occurs in children and is rare in adolescents. It is also uncommon in men older than 70. However, in a study of germ cell tumors in men over 60, 80% of tumors were seminomas. (7) Seminoma is bilateral in about 2% of patients, with bilateral tumors usually being asynchronous. The clinical presentation in most cases is with a testicular mass, but about 10% of patients present with the acute onset of testicular pain and 2.5% present with symptoms related to metastases. There is a history of current or surgically corrected cryptorchidism in 10-30% of patients. At the time of diagnosis 75% of patients have disease limited to the testis, 20% have retroperitoneal spread, and 5% have supradiaphragmatic or organ metastases. Metastases are usually asymptomatic. About 10% of patients have an elevated serum hCG, the prognostic significance of which is not clear. Significant elevations of serum AFP not seen in men with pure seminomas, so an increase in this marker should be taken to indicate that a nonseminomatous component is present somewhere in the tumor or in a metastasis. Serum LDH is also often elevated.

**Pathology**

Grossly, seminomas average 5 cm in maximum dimension, with most measuring between 2 and 6 cm. The tumors are typically soft and fleshy with tan, yellow, pink, or cream cut surfaces. Foci of necrosis with surrounding hemorrhage are common.

Microscopically, there is a characteristic diffuse growth of tumor cells that are separated into nests by variably thick fibrous septa. Lymphocytes are almost always present in the septa and to a lesser extent among the tumor cells. Germinal centers are occasionally seen. Absence of lymphocytes should call the diagnosis of seminoma into question, although rare cases of bonifie seminomas lack a lymphocytic infiltrate. Non-necrotizing epithelioid granulomas are commonly present in the septa, and are seen in more than 50% of tumors. A variety of unusual growth patterns have been described, including an alveolar or pseudoglandular pattern, solid or hollow tubules and cords and trabeculae of tumor cells compressed by stroma. (8) An intertubular pattern of growth is often (36% of cases in one study) seen at the periphery of the tumor (9) or, uncommonly, as the exclusive pattern of growth in a small tumor. (10) Aggregates of lymphocytes sometimes call attention to a small focus of intertubular seminoma that otherwise might go undetected. These small tumors are usually a purely microscopic finding with no grossly visible tumor mass, highlighting the importance of thoroughly evaluating any testis removed from a patient with ITGCNU or a metastatic seminoma with no obvious testicular primary site.

Seminoma cells are round to polygonal with distinct cell borders and moderate to abundant clear or pale to lightly eosinophilic cytoplasm. The cytoplasmic clearing is due to the presence of glycogen, which can be demonstrated with PAS stains in well-fixed material. In some tumors the cells have dense eosinophilic or amphophilic cytoplasm, especially when fixation is less than optimal. A rare finding is the presence of clear cytoplasmic vacuoles that compress the nuclei resulting in a signet ring cell appearance. (11) Seminoma cell nuclei are vesicular, large and central, and have granular chromatin and one or more prominent nucleoli. The uniform distribution of seminoma nuclei contrasts to the disorderly overlapping distribution of nuclei in embryonal carcinoma. Mitotic figures tend to be
numerous. The level of mitotic activity is not correlated with the behavior of the tumor. The category of anaplastic seminoma is no longer accepted as a distinct clinicopathologic entity. There are, however, “atypical” seminomas with increased mitotic activity, greater nuclear pleomorphism, and denser cytoplasm that may be tumors in transition to embryonal carcinoma. The recommended way of handling such cases is to designate them as seminomas unless the tumor cells form glands or papillae or show stronger keratin and CD30 staining than is seen in the background seminoma. (12) Syncytiotrophoblastic giant cells (STGC) are seen on routine histology in 4-7% of seminomas, but staining for hCG reveals a higher incidence, up to 20-25% in some studies. STGC are multinucleated cells with abundant eosinophilic or basophilic cytoplasm and cytoplasmic lacunae. Mononuclear variants exist but are difficult to identify in routine sections. STGC tend to cluster around blood vessels. They are also frequently seen in embryonal carcinoma. The STGC in seminomas are not accompanied by mononuclear trophoblastic cells, as would be seen in choriocarcinoma, and, by themselves, should not be diagnosed as choriocarcinoma. Interestingly, intratubular trophoblastic cells are occasionally identified adjacent to germ cell tumors, almost all of which are seminomas with STGC. (13)

The parenchyma adjacent to a seminoma is almost always abnormal. The seminiferous tubules tend to be atrophic with thick basement membranes and a loss of germ cells that is sometimes sufficient to result in a Sertoli cell only pattern. Intratubular germ cell neoplasia is present adjacent to more than 90% of seminomas. Rete testis involvement is often mentioned in papers on malignant germ cell tumors. I have noted two main patterns of rete testis involvement in seminoma. First, the seminoma can invade the stroma around the rete testis; this is the most important pattern, because it identifies a tumor on the way toward invading the hilar soft tissues. Second, IGCNU or intratubular seminoma can show intratubular or pagetoid spread into the rete tubules themselves.

The H&E morphology of seminoma is fairly distinctive, but I routinely confirm the diagnosis with immunohistochemistry; this not only substantiates the diagnosis, but can highlight occult foci of other patterns of germ cell tumor that might escape notice. Immunohistochemical markers that are useful in seminoma are listed in the table below.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Staining Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT4 (14)</td>
<td>Nuclear</td>
</tr>
<tr>
<td>SALL4 (15)</td>
<td>Nuclear</td>
</tr>
<tr>
<td>NANO (16)</td>
<td>Nuclear</td>
</tr>
<tr>
<td>D2-40 (podoplanin) (16)</td>
<td>Membrane/cytoplasm</td>
</tr>
<tr>
<td>CD117</td>
<td>Membrane/cytoplasm</td>
</tr>
<tr>
<td>PLAP</td>
<td>Membrane/cytoplasm</td>
</tr>
<tr>
<td>hCG</td>
<td>Cytoplasmic staining in STGC</td>
</tr>
</tbody>
</table>

Negative or weak in seminoma: HNF-1, keratin, EMA, CD30, SOX2

Seminomas occasionally undergo partial or complete necrosis, and if regression is complete they can present as a fibrotic nodule in the testis. Sometimes patients with metastatic seminoma undergo orchiectomy and only a fibrotic nodule is found in the testis. This is considered to represent regression of the primary tumor. The testicular nodules are general small, usually less than 2.5 cm and white or tan in color. Microscopically, there is stellate fibrosis, chronic inflammation and atrophy of the surrounding testes. IGCNU or coarse intratubular calcifications are present in more than 50% of cases. (17) In at least half the cases associated with metastatic tumor, the tumor is a seminoma. When necrotic seminoma is present, the tumor type can sometimes be identified with immunohistochemistry. Miller et al reported that OCT4 and CD117 were useful in the classification of necrotic seminomas, (18) but I have found D2-
40 and PLAP to be the most useful for staining necrotic tumor, while OCT4 and CD117 have been generally noninformative, although they do highlight small residual foci of viable seminoma.

The differential diagnosis of seminoma is mainly with embryonal carcinoma, but also includes the solid variant of yolk sac tumor and lymphoma. Histologic features that are helpful in the differential diagnosis between seminoma and embryonal carcinoma are listed in the table below.

<table>
<thead>
<tr>
<th></th>
<th>Nuclear shape</th>
<th>Relationship of Nuclei</th>
<th>Cell borders</th>
<th>Cytoplasm</th>
<th>Stroma</th>
<th>Fibrous septa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma</td>
<td>Round, regular</td>
<td>Uniform spacing</td>
<td>Well defined</td>
<td>Clear or eosinophilic</td>
<td>Lymphs and granulomas</td>
<td>Delicate</td>
</tr>
<tr>
<td>Embryonal Carcinoma</td>
<td>Irregular</td>
<td>Overlapping nuclei</td>
<td>Poorly defined</td>
<td>Amphophilic or basophilic</td>
<td>Not present</td>
<td>None</td>
</tr>
</tbody>
</table>

Immunohistochemical stains are almost invariably used in this differential diagnosis these days. Both seminoma and embryonal carcinoma show positive nuclear staining for OCT4 and SALL4, so these stains are not helpful. However, strong membrane staining for keratin and CD30 is indicative of embryonal carcinoma, as is nuclear staining for SOX2. On the other hand, membrane/cytoplasm staining for CD117 and D2-40 is indicative of seminoma. The solid variant of yolk sac tumor can mimic seminoma. The tumor cells in solid yolk sac tumor tend to be polygonal with clear cytoplasm, thus resembling seminoma cells. However, the nuclei are usually smaller, darker and more primitive appearing than seminoma cells and other more diagnostic patterns of yolk sac tumor are almost invariably present. The potential confusion with seminoma is compounded by the fact that patchy staining for CD117 can be seen in the solid variant of yolk sac tumor. (19) Of course, other markers show the usual staining patterns, so solid yolk sac tumor can stain for AFP, glypican and HNF-1, while seminoma stains for OCT4 and D2-40, neither of which are positive in yolk sac tumor. Some of the histologic variants of seminoma can mimic yolk sac tumor, including those with tubular and microcystic patterns of growth. (8) Immunostains for seminoma and yolk sac tumor markers permit distinction between seminoma and yolk sac tumor in these cases.

**Treatment and Prognosis**

Patients with clinical stage I seminomas can have surveillance or they can be treated with postoperative radiation. There is a relapse rate of 15-20% in patients on surveillance, but successful treatment is possible in almost all patients who relapse, with a survival rate > 99%. It is estimated that surveillance saves 87% of patients from unnecessary radiation. Risk factors for relapse include large tumor size > 4 cm, rete testis invasion and vascular invasion. In stage II, therapy is determined by the size of the metastatic deposits. If the metastases are of limited size, patients are treated with radiation and have a 90-96% survival rate. Patients with bulky retroperitoneal disease are treated with chemotherapy rather than radiation because of high recurrence rates with radiation. The survival rate is lower for patients with bulky disease or stage III, about 80%.

**Spermatocytic Seminoma**

Spermatocytic seminoma is a rare germ cell tumor composed of three types of cells. Despite the name, it does not appear closely related to classical seminoma. (20) There are no lymphocytes or granulomas in the stroma and the tumor cells do not contain glycogen. Spermatocytic seminoma is not associated with ITGCNU or other types of germ cell tumors, and it appears to have a different pathogenesis. The cell of origin is thought to be a spermatogonium. (21) The most consistent
cytogenetic finding is a gain of chromosome 9 and it is postulated that amplification of the DMRT1 (doublesex and mab-3 related transcription factor 1) gene on chromosome 9p24.2 plays a role in tumorigenesis. (22)

Spermatocytic seminoma is reported to account for just over 1% of seminomas. In our practice it is quite rare. I found only one in house case in the UC Hospitals during the last 25 years. Patients with spermatocytic seminoma tend to be older than those with usual seminoma and other germ cell tumors. The average age is in the mid 50's, but spermatocytic seminoma occurs over a wide age range and can be found in younger patients. The typical clinical presentation is with painless testicular enlargement. 9% of spermatocytic seminomas are bilateral, and these are usually asynchronous. Rare spermatocytic seminomas undergo sarcomatous transformation.

Pathology
Spermatocytic seminoma is similar in size to conventional seminomas. The cut surfaces are edematous to gelatinous and they are soft and tan or gray.

At low magnification the tumor has a multinodular or diffuse pattern. The tumor cells grow in sheets or nests within the nodules. The stroma tends to be edematous and pools of hydric edema fluid can separate the cells into clusters or trabeculae or even single cells. Accumulations of fluid result in formation of cysts or pseudoglands. Lymphocytic infiltrates and granulomas, which are characteristic features of seminoma, are not present in spermatocytic seminoma.

Spermatocytic seminoma is composed of 3 types of cells. small, medium sized, and giant. Medium sized cells predominate and have a round nucleus with finely granular chromatin and modest cytoplasm. Small cells somewhat resemble lymphocytes as they have a densely basophilic nucleus and scant eosinophilic cytoplasm. These cells may be degenerative. Large or giant cells are the third cell type present. They have one or multiple nuclei, variably prominent nucleoli and filamentous chromatin similar to that seen in primary spermatocytes in meiotic prophase. Mitotic figures are frequent and there are many apoptotic cells.

Tumors in which there is diffuse proliferation of intermediate sized cells with prominent nucleoli have been called anaplastic variants of spermatocytic seminoma; these could potentially be confused with embryonal carcinoma. (23) Sarcomas, mainly rhabdomyosarcoma or undifferentiated sarcoma, arise in about 6% of cases and are a prognostically highly significant finding. (24)

Spermatocytic seminoma lacks staining for most standard germ cell markers. The tumor cells are negative for OCT4, AFP, HCG, and CD30 and PLAP is absent or present only in rare cells. Keratin stains are negative except for dot like staining with CK18. Spermatocytic seminoma is positive for SALL4, (15) and CD117 is positive in 50-60% of tumors.

Treatment and Prognosis
The prognosis is excellent with only two reports of cases that have metastasized to retroperitoneal lymph nodes. The anaplastic variant has the same favorable prognosis as standard spermatocytic seminoma. Standard and anaplastic spermatocytic seminomas are therefore treated by orchiectomy without chemotherapy or radiation. Cases in which the tumor shows sarcomatous transformation on the other hand behave aggressively and have a poor outcome.

Embryonal Carcinoma
Embryonal carcinoma is a type of testicular tumor composed of anaplastic primitive epithelial cells arranged in a variety of patterns. It is uncommon to find a pure embryonal carcinoma in the testis. In the literature about 5% of pure testicular germ cell tumors are embryonal carcinomas, but 40% of all germ cell tumors and 87% of all nonseminomatous germ cell tumors have an embryonal carcinoma component. In a recent large pathologic study of embryonal carcinoma in a consultation practice, 16%
of tumors were pure embryonal carcinomas and 84% were mixed germ cell tumors with an embryonal carcinoma component. (25)

Embryonal carcinoma occurs in young men about 10 years younger, on average, than those with seminoma. Most patients are in the age range of 25-35 years, with an average of 32 years old at diagnosis. Embryonal carcinoma is not reported to occur in prepubertal children and it is rare in teens less than 15 years of age. Most patients (80%) present with a testicular mass that may cause pain or discomfort. About 10% of patients present with metastases and 10% with hormonal symptoms, the most common of which is gynecomastia.

Only about 40% of patients have disease confined to the testis at diagnosis. Another 40% have retroperitoneal lymph node metastases and 20% have supradiaphragmatic lymph node metastases or visceral organ spread. Patients with pure embryonal carcinoma usually do not have an elevated serum AFP, but serum hCG is elevated in 60% of patients due to secretion of the hormone by syncytiotrophoblastic cells within the tumor. A majority of patients with advanced disease have an increased serum LDH.

Pathology

Embryonal carcinoma is usually smaller and less well defined than seminoma. The average size is 2.5 cm. The cut surface of the tumor is soft and gray, pink or tan with foci of hemorrhage and necrosis. There is local invasion into the rete and the epididymis in about 25% of patients.

Microscopically, the tumor consists of cohesive groups of large epithelial cells. Solid sheets of tumor cells are present in almost every tumor and variably well-formed glands and papillae are also frequently present. A variety of uncommon growth patterns have been described including nested, micropapillary, anastomosing glandular, sieve-like glandular and pseudopapillary. (25) Embryonal carcinoma is also a component of tumors with a polyembryoma or diffuse embryoma growth pattern.

Embryonal carcinoma cells are polygonal, cuboidal or columnar. They have moderate to abundant cytoplasm that varies in its tintorial properties, ranging from basophilic to amphiphilic to eosinophilic. The tumor cell nuclei are large and vesicular with irregular coarse chromatin and prominent parachromatin clearing. The nuclei contain one or more large nucleoli that often appear to overlap. The nuclei are variable in size and shape, and they do not have the uniform spacing that characterizes seminoma; the nuclei are frequently overlapping. Mitotic figures numerous. Degenerated tumor cells can be numerous and if they are condensed around the periphery of the tumor cell nests, as often happens, the histologic picture can mimic choriocarcinoma. Intratubular embryonal carcinoma is present adjacent to the invasive tumor in about 25% of cases. The intratubular component is often partly or even completely necrotic and it may contain large calcifications. Embryonal carcinoma commonly invades blood or lymphatic vessels and when an angioinvasive component is found in a mixed germ cell tumor it consists of embryonal carcinoma in a disproportionate number of cases. Syncytiotrophoblastic giant cells (STGC) are a very common finding in embryonal carcinoma and are the source of the increased serum hCG noted in many of these patients. In some tumors, the stroma is fibrous and typically of low cellularity and is judged to be non-neoplastic. In a significant minority of tumors, the stroma is composed of primitive mesenchymal cells or atypical smooth muscle cells, and is thought to be neoplastic. In the past, a neoplastic spindle cell stroma was often viewed as an intrinsic feature of embryonal carcinoma and many still view it that way. Kao and Ulbright, on the other hand, favor classifying it as teratomatous based on its likely resistance to chemotherapy. (25)

Embryonal carcinoma almost always shows positive nuclear staining for OCT4. (14) SALL4 (15) and SOX2 (26) are generally positive as well although SOX2 and SALL4 also show staining in teratomas, especially in primitive neuroectodermal tissues. Most embryonal carcinomas are keratin positive, with a membrane staining pattern, and there is diffuse membrane staining for CD30 in almost all cases as well. AFP staining has been reported as present in a minority of embryonal carcinomas, from 8-33%. Some of
the staining reported in older series was probably in yolk sac tumor elements, not embryonal carcinoma. Nevertheless, occasional cases of embryonal carcinoma in a mixed germ cell tumor show positive staining of scattered tumor cells, mostly in areas with a solid pattern. PLAP and D2-40 can be positive in embryonal carcinoma, but staining is more focal and weaker than in seminoma, and the two are not likely to be confused based on staining for PLAP or D2-40.

A majority of cases of embryonal carcinoma contain an isochromosome i12p or show 12p amplification. In general, light microscopy and immunohistochemistry are adequate to diagnose embryonal carcinoma, and in situ hybridization studies for the i12p are not commonly used for diagnosis. However, evaluation for an i12p could be useful for the differential diagnosis of an undifferentiated carcinoma at a metastatic site.

The main differential diagnosis is with yolk sac tumor. For diagnosis of a yolk sac tumor it is necessary to identify one of the distinctive histologic patterns of yolk sac tumor. Immunohistochemistry can be helpful in this differential diagnosis as well. Choriocarcinoma can enter the differential diagnosis, particularly when numerous STGC are present in the tumor. Embryonal carcinoma lacks a true biphasic pattern and the tumor cells are OCT4 positive and HCG negative. Finally, lymphoma and melanoma are occasional considerations.

<table>
<thead>
<tr>
<th>Stain</th>
<th>Embryonal Carcinoma</th>
<th>Yolk Sac Tumor</th>
<th>Choriocarcinoma</th>
<th>Lymphoma</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT4</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SALL4</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOX2</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratin</td>
<td>+, membrane</td>
<td>+, cytoplasm</td>
<td>+, cytoplasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD30</td>
<td>+, membrane</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hCG</td>
<td>+, in STGC</td>
<td></td>
<td>+, in STGC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCA</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>S100, SOX10</td>
<td></td>
<td></td>
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<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Treatment and Prognosis

In general, embryonal carcinoma and other nonseminomatous tumors are treated similarly, so these comments apply to nonseminomatous germ cell tumors in general. The main treatment options in early stage disease (stage I) are active surveillance, retroperitoneal lymph node dissection, and adjuvant BEP chemotherapy (1 or 2 courses). In one recent large study from Denmark, all patients with stage I nonseminomatous germ cell tumors were placed on active surveillance (1226 patients). (27) The relapse rate after orchiectomy was 30.6%. Three main risk factors were identified: vascular invasion, rete testis invasion, and presence of any amount of embryonal carcinoma. A high risk group with all 3 (embryonal carcinoma, vascular invasion and rete testis invasion) had a relapse rate of 50% while a group with none of these risk factors had only a 12% recurrence rate. 80% of the relapses occurred in the first year after treatment and only 1.6% of patients had a relapse after 5 years. The disease specific survival at 15 years was 99.1%. Basically, modern chemotherapy has eliminated the survival differences among different treatment groups and almost all patients with early stage disease are successfully treated. What can vary is the amount of chemotherapy that is administered and whether or not surgery is performed. In practice here in the US, patients with clinical stage I tumors have an excellent outcome with 98-100% survival. In general, patients with stage IA tumors are placed on active surveillance and those with stage IS receive chemotherapy. Management of stage IB is more varied, and includes surveillance, one or two courses of BEP adjuvant chemotherapy or retroperitoneal lymph node dissection. (28)
In the United States, most patients who have known retroperitoneal involvement of limited extent have a retroperitoneal lymph node dissection, followed by chemotherapy or surveillance. The survival is about 98%. Patients with advanced disease, such as bulky retroperitoneal lymph nodes or distant metastases, are treated with chemotherapy followed by surgical resection of any residual masses that are present. This results in a survival of 70-80%. The presence of viable appearing nonteratotamous germ cell tumor elements in postchemotherapy masses identifies a group at high risk for relapse, with a relapse rate of up to 42% in one series. In a good risk patient population, only 5-6% of patients have residual malignant germ cell tumor in postchemotherapy retroperitoneal masses, 30-60% have residual teratoma, and the rest have no identifiable tumor. (29)

Risk factors for relapse have been identified in large clinical studies and these should be documented as present or absent in the pathology report. In the large Danish study mentioned above, three risk factors were identified, vascular invasion, the presence of embryonal carcinoma, and rete testis involvement. (27) An earlier English study identified the presence of yolk sac tumor as a favorable finding that lowered the risk of recurrence. (30) In a study of nonseminomatous germ cell tumors of all stages, Yilmaz et al identified vascular invasion, rete testis invasion and hilar soft tissue invasion as risk factors associated with metastases. (31) Using a cutoff of 50% or more of the tumor as significant, they did not confirm embryonal carcinoma as a risk factor, in contrast with most previous studies, although most studies have focused on clinical stage I disease.

<table>
<thead>
<tr>
<th>Risk Factors for Recurrence/Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular invasion</td>
</tr>
<tr>
<td>Rete testis involvement (invasive tumor between the tubules)</td>
</tr>
<tr>
<td>Hilar soft tissue involvement</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
</tr>
<tr>
<td>Absence of yolk sac tumor (presence of YST appears to be a favorable finding in primary tumors)</td>
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Pathologists should be aware that the antigenicity of embryonal carcinoma may be altered post-chemotherapy. In one study of 25 cases of postchemotherapy metastatic embryonal carcinoma, 19 (75%) were positive for OCT4, but only 8 showed diffuse strong staining for CD30. (32) Six cases (24%) were negative for both markers, but showed the usual membrane pattern of staining for AE1/AE3. Thus, one or more markers may be lost and it is necessary to perform a panel of stains to establish the correct diagnosis. We recently encountered such a case, but were able to make the diagnosis based on the characteristic H&E morphology and the pattern of staining for keratin.

Yolk Sac Tumor

Yolk sac tumor is a primitive germ cell tumor that differentiates to form structures typical of the embryonic yolk sac, the allantois and the extraembryonic mesenchyme. Yolk sac tumor is the most common testicular tumor of children, accounting for 48-62% of such tumors, which is twice the frequency of the second most common tumor, which is teratoma. It arises at a median age of 16-20 months and 75% are found in children less than 2. It rarely occurs in children older than age 4. In contrast to juvenile granulosa cell tumor, it is rarely if ever congenital. In children, it is almost always a pure tumor that presents in clinical stage I.

In postpubertal patients yolk sac tumor is usually a component of a MGCT. Most tumors are detected in patients 15-40 years of age. In one recent large series, 6% of pure nonseminomatous germ cell tumors were yolk sac tumors and 53% of mixed germ cell tumors had a yolk sac tumor component. (31) Interestingly, in adults, the presence of yolk sac tumor in a testicular germ cell tumor seems to be a favorable prognostic finding and nonseminomatous germ cell tumors with a yolk sac tumor component
are more likely to be clinical stage I. Both adult and pediatric yolk sac tumors are generally associated with a significant elevation of the serum AFP.

**Pathology**

Yolk sac tumors are gray white, tan, or yellow and they have mucoid cut surfaces with variably sized cysts.

Microscopically, yolk sac tumor frequently poses diagnostic problems because there are so many different histologic patterns. The most common and easiest to recognize are the reticular pattern and the endodermal sinus pattern. The various patterns are summarized in the table below:

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Description</th>
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<tbody>
<tr>
<td>Reticular</td>
<td>Anastomosing thin cords of tumor cells that surround spaces, or single cells with large intracytoplasmic vacuoles result in a microcystic or net like pattern.</td>
</tr>
<tr>
<td>Macrocytic</td>
<td>Larger cystic spaces are present in the tumor.</td>
</tr>
<tr>
<td>Endodermal sinus (festoon)</td>
<td>Labyrinthine spaces are lined by cuboidal to columnar cells. This pattern contains the endodermal sinus like structures known as Schiller Duval bodies.</td>
</tr>
<tr>
<td>Papillary</td>
<td>The tumor grows in a papillary pattern with or without fibrovascular cores in the papillae.</td>
</tr>
<tr>
<td>Solid (19)</td>
<td>Sheets of polygonal cells, sometimes with clear cytoplasm. Can mimic seminoma. Can be highly vascular. This pattern occasionally consists of sheets of small dark staining cells resulting in a blastema like appearance.</td>
</tr>
<tr>
<td>Glandular-alveolar</td>
<td>A pattern composed of enteroblastic, enteric or endometrioid like glands. The glands often connect with cystic spaces resulting in overlap with the polyvesicular vitelline pattern. The glands are branching and anastomosing or tubular and often have enteric features with goblet cells or basal vacuoles like in early secretory endometrium. The nuclei of the glandular cells can be less atypical than those of adjacent nonglandular components. Purely glandular tumors of endometrioid or intestinal type can occur, and can be associated with very high serum alpha-fetoprotein levels.</td>
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<tr>
<td>Myxomatous</td>
<td>This pattern tends to be associated with the reticular pattern. It consists of keratin positive spindled cells in a myxoid background. The spindle cells are pluripotent and can differentiate into skeletal muscle and cartilage. Scattered foci of somatic differentiation as generally accepted in yolk sac tumor, but if nodules of differentiated mesenchyme are present they are viewed as teratomatous.</td>
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<tr>
<td>Sarcomatoid</td>
<td>Rare yolk sac tumors have a cellular spindle cell component that is usually keratin positive.</td>
</tr>
<tr>
<td>Polyvesicular Vitelline (PVV) (33)</td>
<td>The PVV pattern consists of cysts scattered in a variably cellular mesenchyme. Some show eccentric constrictions resulting in a flask like appearance. The cysts are lined by flattened to columnar epithelium. The PVV pattern is rare in testicular tumors.</td>
</tr>
<tr>
<td>Hepatoid</td>
<td>Hepatoid cells are seen in about 20% of yolk sac tumors, mainly as small clusters of liver like cells. Occasionally, this pattern is more extensive. It consists of polygonal cells with abundant eosinophilic cytoplasm. Bile can sometimes be identified in the cytoplasm or in canaliculi between the cells. Hepatoid foci are strongly positive for alpha-fetoprotein. Hyaline globules are particularly common in hepatoid foci.</td>
</tr>
<tr>
<td>Parietal</td>
<td>The parietal pattern consists of eosinophilic bands and sheets of basement membrane material in the extracellular space between the neoplastic cells. It is thought to resemble the parietal layer of the embryonic yolk sac of the rodent. It is common but usually only a focal finding.</td>
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Hematopoietic elements are occasionally noted in yolk sac tumors. Erythroblasts in blood vessels or in the mesenchymal component are the usual histologic finding. Adult and pediatric tumors are similar in morphology but a major difference between them is the presence of IGCNU in tubules adjacent to adult tumors; IGCNU is absent in pediatric cases.

Immunohistochemistry is generally used in the evaluation of yolk sac tumors. Alpha-fetoprotein was one of the first stains to be used for this purpose and staining for AFP can still be considered to be one of the gold standards for the diagnosis. AFP is positive in 75-100%, but staining is often focal and weak, which can result in absent staining in small foci of yolk sac tumor or in small biopsy samples. Hepatoid foci stain intensely for AFP. SALL4 and glypican 3 are almost always positive with a nuclear staining pattern for SALL4 and cytoplasmic and membranous staining with glypican. (15, 34, 35) The embryonal carcinoma markers OCT4 and CD30 are negative. Keratin is positive with a cytoplasmic staining pattern, but EMA and CK7 are almost always negative. Vimentin stains the spindle cell component, if present, which is also often keratin positive. Staining for PLAP is reported to be variable. The solid pattern of yolk sac tumor can show staining for CD117, which can cause confusion with seminoma, and AFP is frequently negative in the solid pattern of yolk sac tumor, so these two stains cannot be used to differentiated between solid yolk sac tumor and seminoma. (19) Some stains that are not generally thought of a yolk sac tumor stains are highly expressed in these tumors, including RCC and hepatocyte nuclear factor-1 beta (HNF-1). I frequently use the latter as an additional yolk sac marker; it shows nuclear staining in yolk sac tumor.

The differential diagnosis depends on the patient age. In children, juvenile granulosa cell tumor is the main problem. Immunohistochemical stains for yolk sac tumor and sex cord stromal tumor markers resolve most cases. It is worth noting that the serum AFP is not much help in very young children since the serum AFP does not fall into the normal adult range until about 8 months of age.

In adults it is critical that pathologists differentiate accurately between the solid variant of yolk sac tumor, which can have clear cells, and seminoma, since these tumors may be managed differently. A purely glandular yolk sac tumor could potentially be confused with a teratoma. Helpful features include that the enteric glands in yolk sac tumors tend to lack a circumferential smooth muscle component and often branch extensively, while in teratomas a band of smooth muscle often surrounds enteric glands. Yolk sac tumor glands are AFP positive and negative for EMA and CK7, while teratoma glands generally show the opposite pattern, although it should be noted that limited AFP staining can be seen in teratoma glands and of course liver tissue in teratomas is AFP positive.

**Treatment and Prognosis**

Pediatric patients are usually managed conservatively with surveillance if clinical disease is limited to the testis and there is no elevation of the serum AFP. Chemotherapy is administered only if a relapse is detected. Pediatric yolk sac tumors are less aggressive than their adult counterparts. Retroperitoneal lymph node metastases are uncommon (4-14%) and if the tumors spread metastasis via hematogenous routes is more common. (36) Almost all children who have recurrences, which are usually in the lungs, are effectively managed with cisplatin based chemotherapy. Some pediatric yolk sac tumors do not cause an elevated serum AFP, which can make early detection of recurrences difficult.

The treatment in adult patients is the same as for embryonal carcinoma and other nonseminomatous germ cell tumors. Adults with clinical stage I tumors that have a yolk sac tumor component are less likely to relapse than those that do not contain yolk sac tumor. On the other hand, in stage III disease, patients with a yolk sac tumor component in their neoplasm have a poor prognosis. This is interpreted as indicating that yolk sac tumor has less metastatic potential than other nonseminomatous germ cell tumors but it is less chemosensitive than embryonal carcinoma. Autopsy studies of patients with germ cell tumors show a much higher frequency of residual yolk sac tumor components now than was the case before effective chemotherapy was developed.
In a review of somatic like malignancies arising in germ cell tumors, 7 of 45 glandular tumors were reclassified from adenocarcinomas to glandular yolk sac tumors and 26 of 76 sarcomatoid tumors were reclassified as sarcomatoid yolk sac tumors. (37, 38) These studies indicate that a significant proportion of tumors that might be suspected of being secondary malignancies are in fact variants of yolk sac tumor, and pathologists should keep this in mind when evaluating such neoplasms.

**Choriocarcinoma**

Choriocarcinoma is a highly malignant tumor that is composed of an admixture of multinucleated syncytiotrophoblastic cells and mononuclear trophoblasts. Pure choriocarcinoma is very rare, accounting for less than 1% of testicular tumors; some large series contain no cases of pure choriocarcinoma. Choriocarcinoma mainly occurs as a component of a mixed germ cell tumor and is found in 8-9% of such tumors. Pure choriocarcinoma or choriocarcinoma predominant mixed germ cell tumors are much less common. In one recent series of 1010 cases, there were 6 (0.6%) pure choriocarcinomas and 9 (0.9%) choriocarcinoma predominant mixed germ cell tumors. (39)

Choriocarcinoma occurs mainly in patients from 20 to 40 years; it is not reported in prepubertal boys. It is prone to give rise to hematogenous metastases and patients whose tumors contain choriocarcinoma are more likely to present with metastases than with symptoms caused by the primary testicular tumor. Almost all patients have metastases at diagnosis. Common clinical presentations include hemoptysis due to lung metastases, back pain due to retroperitoneal spread, GI bleeding due to metastases to the gastrointestinal tract and neurologic symptoms due to brain metastases. The lungs, liver and brain are the most common sites. Hemorrhagic metastases of choriocarcinoma cause a constellation of findings that are sometimes referred to as the “choriocarcinoma syndrome.” Rare patients present with skin metastases that can mimic squamous cell carcinomas.

Patients with choriocarcinoma typically have marked elevations in the serum hCG, with levels exceeding 100,000 IU/L not uncommon in cases of pure choriocarcinoma. Hormonal abnormalities, mainly gynecomastia, are observed in about 10% of cases and rare patients with high serum hCG levels have had thyrotoxicosis.

**Pathology**

The testis may not be enlarged in the rare pure cases since the tumors are small. Grossly, there are one or multiple hemorrhagic necrotic nodules.

The microscopic appearance corresponds with the gross in that choriocarcinomas are extensively hemorrhagic and necrotic with little viable tumor; viable tumor is most likely to be at the periphery. These tumors are composed of a mixture of syncytiotrophoblastic (STGC) and mononuclear trophoblastic cells resulting in a characteristic intertwining biphasic pattern. Among the mononuclear trophoblastic cells, there are smaller cells thought to be cytotrophoblasts and larger cells with ample cytoplasm more in keeping with intermediate trophoblastic cells. The STGC most often overlay nests or columns of mononuclear trophoblastic cells but sometimes the two cell types seem randomly mixed. Other tumors have an inconspicuous STGC component resulting in a monophasic appearance. Blood vessel invasion is common.

The STGC have several to numerous vesicular to hyperchromatic nuclei and abundant cytoplasm with distinct cytoplasmic vacuoles. In some tumors multinucleation is less prominent, but the syncytiotrophoblastic cells have giant nuclei. Small STGC that are hard to distinguish from mononuclear cells are occasionally noted and the difference in the cytoplasm may be all that distinguishes them. Mitotic figures are not present in STGC.

The mononuclear trophoblastic cells have pale cytoplasm, mildly pleomorphic nuclei, prominent nucleoli and discrete cell borders. Depending on their size and cytoplasmic features they can resemble cytotrophoblasts or intermediate trophoblasts. Tumors in which the mononuclear cells resemble
intermediate trophoblasts have less of a biphasic in appearance since the mononuclear cells are larger and are more similar in size to the STGC.

hCG is the most useful immunohistochemical marker for choriocarcinoma. STGC and some mononuclear cells show positive cytoplasmic staining while cytotrophoblastic cells are negative or at most show weak staining. P63 is positive in the smaller mononuclear cytotrophoblastic trophoblastic cells and HPL is positive in STGC and some large intermediate trophoblastic cells. (39) Inhibin and EGFR are both positive in STGC, as is glypican-3. Patchy staining for PLAP is reported in about half of tumors. Cytokeratin AE1/AE3 shows strong cytoplasmic staining in all cell types in choriocarcinoma. CK7 stains many cells in contrast to the generally negative staining seen in most other germ cell tumors. Reportedly, EMA stains STGC.

The differential diagnosis includes other tumors that can contain STGC, including seminoma and embryonal carcinoma. In seminoma, the STGC are single cells or loose aggregates in the characteristic background of seminoma cells, fibrovascular septae and lymphocytes. STGC are even more common in embryonal carcinoma than in seminoma, but here the background is embryonal carcinoma cells, not trophoblastic cells. Some embryonal carcinomas contain condensed degenerated tumor cells at the periphery of cell nests that mimic STGC and can thus cause confusion with choriocarcinoma. In all of these settings, appropriate immunohistochemical staining resolves the diagnosis.

There are rare (at least 2) reports of testicular tumors that resemble placental site trophoblastic tumors. Both reported patients were well after orchiectomy. The diagnosis of a tumor that resembles a placental site trophoblastic tumor (PSTT) should be made only when the tumor consists entirely of intermediate trophoblastic cells. Some choriocarcinomas contain a predominance of intermediate trophoblastic cells, but they also contain more numerous syncytiotrophoblastic cells.

An unusual form of cystic trophoblastic tumor has been described, occurring mainly in metastatic sites after chemotherapy of a germ cell tumor that may or may not have contained choriocarcinoma. This pattern has also been seen in primary mixed germ cell tumors lacking a choriocarcinoma component. It consists of cysts lined by one or multiple layers of squamoid trophoblastic cells with eosinophilic cytoplasm. The cysts contain blood or are empty. Stains for hCG are only focally positive. When seen at metastatic sites after chemotherapy the clinical course has been similar to teratoma, so this pattern does not appear to be an adverse prognostic finding in that setting.

**Treatment and Prognosis**

A tendency for widespread hematogenous metastases results in a worse prognosis for pure or predominant (> 50%) choriocarcinoma than for other germ cell tumors. Of 14 patients with followup, 11 died of tumor despite receiving BEP chemotherapy, 1 was alive with disease and 2, both with metastatic disease limited to the lungs, were alive with no evidence of disease. (39) It is not clear what minimum percentage of choriocarcinoma must be present in a tumor for it to be considered high risk.

**Teratoma**

Teratoma is a tumor of germ cell origin that differentiates to form somatic tissues of adult or embryonic type. Pure teratomas account for only 3-4% of germ cell tumors, but of course teratoma is a common constituent of mixed germ cell tumors.

Teratomas occur in two age groups. Prepubertal teratomas are the second most common germ cell tumor of infancy and childhood, after yolk sac tumor, accounting for ~30% of cases. The median age is 13m and most occur in boys younger than 4 years. Teratomas are almost always pure in this age group and the clinical behavior is benign. Patients can be treated by orchiectomy alone. In assessing and following young patients it should be remembered that the serum AFP levels do not drop to adult levels until around 8 months of age.
In adults teratomas occur in the same age range as other malignant germ cell tumors. Pure teratomas are uncommon but they are reported to behave in a malignant fashion. For example, in one report, 37% of referred patients presented with advanced disease and of patients with low stage pure testicular teratomas 40% were found to have retroperitoneal lymph node metastases and 16% had a relapse after retroperitoneal lymph node dissection. (40) In another study of pure teratomas, 6 of 14 patients had retroperitoneal lymph node metastases at diagnosis or on followup. (41) In the testis teratoma is most commonly found mixed with other germ cell elements. About half of mixed germ cell tumors have a teratoma component. It is not unusual for patients with testicular teratomas to develop metastases that contain nonteratomatous germ cell elements. (42) Presumably this is because teratomas develop from primitive germ cell tumors that may metastasize but also regress or differentiate to a teratoma in the testis. Ovarian teratomas are subclassified as mature or immature, with only the latter being viewed as malignant. In the testis there have been no demonstrated differences in behavior between mature and immature teratomas, so they are all simply classified as teratomas.

Most patients with teratomas present with a testicular mass. The reported frequency of metastases in patients with pure teratomas has ranged from 20 to 46% but the cases have all been from referral centers and the series are likely biased. Tumor markers are generally negative, although slight elevations of alpha-fetoprotein might be detected in patients whose teratomas contain hepatic tissue or endodermal tissues that show immunohistochemical staining for AFP.

Pathology

Pure teratomas and areas of teratoma in mixed germ cell tumors that are large enough to identify grossly are nodular and they are usually solid with cystic spaces.

Microscopically, prepubertal teratomas often consist of tissues with organoid morphologies such as well formed gastrointestinal tubes that include a surrounding smooth muscle layer. Pancreatic tissue with islets and ducts may also be present. A more random mixture of elements may also be seen. Immature tissues are less common than in postpubertal cases. There is no significant atypia, mitotic figures are generally rare and IGCNU is not identified in the adjacent testis, implying a different pathogenesis than for teratomas in adults.

Postpubertal teratomas contain a random distribution of tissues from multiple germ layers. Common findings include squamous epithelium, enteric type glandular epithelium lined by absorptive and goblet cells or columnar mucinous cells, and glands lined by respiratory epithelium. Some glands have a complex, branching architecture. Nests of transitional epithelium are common and pigmented retinal type epithelium can sometimes be identified. Tissues that are not commonly present in testicular teratomas include pancreas, thyroid, prostate, and choroid plexus. Rupture of keratin cysts results in inflammation with foreign body giant cells. Incomplete organoid differentiation may be present, with smooth muscle partly or completely encircling glands or bronchi. Common stromal tissues include smooth muscle, fibrous tissue, and cartilage. Adipose tissue and bone are less common. Immature elements are most often neuroectodermal and less often nephroblastic. Immature neural cells form tubules or rosettes or grow in diffuse sheets. In immature renal tissue blastema can be mixed with primitive tubules somewhat mimicking a nephroblastoma. IGCNU is present in the seminiferous tubules adjacent to the tumor in 90% of cases, and the parenchyma is often abnormal with loss of spermatogenesis and tubular and peritubular sclerosis.

Significant cytologic atypia can be present in various elements of both mature and immature types in adult teratomas, with nuclear enlargement, hyperchromasia and occasional mitotic figures. We recently encountered a teratoma in which there was significant atypia of chondroid elements.

Worrisome embryonic rhabdomyoblastic elements, foci of more differentiated fetal type skeletal muscle or other sarcomatoid appearing stromal tissues may be present in teratomas, raising the
differential diagnosis of immature elements vs a secondary malignancy developing in a teratoma. If the areas in question are small, do not show significant stromal overgrowth, and interweave with other structures they are classified as immature elements. On the other hand, if they are more extensive, exceeding one low power (4x) microscopic field in size, sarcomatoid areas are best classified as a secondary malignancy. In general, areas of sarcomatous transformation are fairly extensive.

Immunohistochemistry is not used much in the evaluation of teratomas. Alpha-fetoprotein can be found in glands of enteric or respiratory type and in hepatic type cells. Glypican 3 stains immature elements and both SOX2 and SALL4 show staining of immature neuroectodermal elements of 80%. OCT4 is negative in these elements. Interestingly, comparative staining of male and female teratomas for the “cancer” marker IMP3 revealed lack of staining in mature female teratomas but positive staining in all primary and metastatic mature testicular teratomas, in keeping with the benign nature of the former and the malignant nature of testicular teratomas. (43)

Postpubertal teratomas tend to be aneuploid and have an i12p. In one study, 12p abnormalities were demonstrated in 72% of pure testicular teratomas, and in the fibrous stroma of the tumor. (44) Prepubertal teratomas are diploid and have normal cytogenetic findings.

Several specialized cystic teratomatous tumors occur in the testis, including dermoid cysts and epidermoid cysts.

A dermoid cyst is accepted as a type of teratoma. It is a cystic tumor in which the cyst lining has a skin like epidermal surface with underlying dermal type tissue that contains adnexal structures including hair follicles and sebaceous glands. Dermoid cysts lack immature elements, there is no IGCNU in the testicular tubules next to them and the morphology of the background testis is normal with normal spermatogenesis. A lipogranulomatous reaction in the parenchyma adjacent to the lesion favors a dermoid cyst. Benign mature tissues other than skin and skin appendages may be present, including glandular epithelium with goblet cells, cartilage, fibrous tissue and glia. Some tumors have a pilomatrixoma like appearance. (45)

Recently, Zhang et al reported a small series of benign mature teratomas that included dermoid cysts and mature teratomas that were composed of well-formed tissues that often had an organoid appearance (for example, ciliated respiratory epithelium surrounded by a cuff of smooth muscle). (46) Squamous cysts or squamous cells were often present, but adnexal structures were not seen except in the dermoid cysts. Both the dermoids and the other benign teratomas, which histologically resembled prepubertal teratomas, lacked adjacent IGCNU, showed normal spermatogenesis, lacked tubular atrophy or sclerosis, lacked scarred zones or microlithiasis, showed no cytologic atypia and were demonstrated to lack increased 12p material. If an i12p is identified or there is IGCNU in the background testis the tumor is not a benign teratoma.

Epidermoid cysts are cysts that are lined by histologically benign stratified squamous epithelium and filled with laminated keratin. (47) There are no cutaneous adnexal structures or other types of tissue, no atypia and no associated IGCNU or abnormalities of the background testis. Epidermoid cysts have a benign clinical behavior.

Treatment and Prognosis

Selected benign teratomas such as dermoid cysts may be adequately treated by local excision, but some surrounding normal testis must be present for examination in order to validate the benign nature of the tumor. Most teratomas are treated by orchiectomy. The behavior of postpubertal teratomas is difficult to predict because the survival results that have been reported have been quite variable. The British Testicular Tumor Panel found that 2 of 12 adult patients died of tumor. The presence of mature teratoma in a primary testicular tumor correlates with a decreased likelihood of occult metastases.
When pure teratoma is the only element found in metastatic sites the outcome is favorable except in cases where there is a secondary malignancy. Disease free survival rates of 87-94% have been reported after resection of pure teratomatous metastases. Such lesions should nevertheless be removed because they are genetically unstable and can give rise to secondary malignancies. Also, they can progressively enlarge and cause symptoms or death due to local effects, a process referred to as the growing teratoma syndrome. The growing teratoma syndrome is defined as an increase in the size of a metastatic tumor during or after chemotherapy with only a teratoma component being found on histological analysis of the resected tumor. If the metastatic tumor is completely resected it is unlikely to recur, but if it is incompletely resected recurrence is probable.

A secondary malignancy occasionally arises in a teratoma at the primary site in the testis or in a metastatic site. (48) The preferred terminology is to designate such tumors as a teratoma with a secondary malignant component. The sarcoma may be detected in the testis, in a metastatic site, or both. (49) Most represent excessive proliferations of embryonic type atypical elements that form neoplastic masses resembling primitive neuroectodermal tumors, (50) nephroblastomas, or some other blastomatous neoplasm. Rhabdomyosarcoma is the most common type of secondary sarcoma. (51) Molecular pathologic studies indicate that the same abnormalities (12p abnormalities and loss of heterozygosity) are present in the teratoma and the secondary malignant component, demonstrating a common progenitor cell. (52) The criterion for differentiating between a teratoma with a large amount of immature tissue and one with a secondary malignant component is that in the latter there is overgrowth of the tumor by a pure population of the atypical element larger in size than a single 4x low power field. Rarely, somatic type carcinomas develop and these are recognized by the presence of cytologic atypia, mitotic activity and stromal invasion with desmoplasia. The significance of a secondary malignancy is unclear. A secondary malignant component in the primary tumor does not necessarily confer a worse prognosis. However, when a secondary malignancy develops at a metastatic site, usually after chemotherapy, it is associated with a poor outcome. (49)

Mixed Germ Cell Tumor

Tumors composed of mixtures of germ cell tumor elements are extremely common. In a Danish registry of sequential tumors, 69% of nonseminomatous tumors and 32% of all cases were mixed germ cell tumors (MGCT). In a recent study from Canada, 78% of all nonseminomatous germ cell tumors were MGCT. (31) The average age of patients with MGCT is around 30; patients whose tumors contain a predominance of embryonal carcinoma are slightly younger and those with a predominance of seminoma are slightly older.

Two types of MGCT are specifically classified – polyembryoma and diffuse embryoma. Polyembryoma is composed of embryonal carcinoma and yolk sac tumor, often admixed with teratomatous elements. The tumor contains structures that resemble a presomatic embryo prior to day 18 of development. A central plate consists of embryonal carcinoma, there is a dorsal amnion like cavity lined by flattened cells, and a ventral yolk sac like area composed of reticular and myxomatous yolk sac tumor. The embryoid bodies are less than a mm in size and are surrounded by myxoid embryonic mesenchyme. The well-defined architecture can break down with overgrowth of the yolk sac tumor and embryonal carcinoma elements. Diffuse embryoma is a tumor that is composed of an intimate admixture of approximately equal parts of embryonal carcinoma and yolk sac tumor, sometimes with minor trophoblastic or teratomatous elements. (53) The yolk sac tumor appears draped around the embryonal carcinoma.
References

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