Sex Cord-Stromal Tumors of the Testis

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Sex cord stromal neoplasms are uncommon testicular tumors, accounting for only a few percent of all testicular tumors. These tumors occur over a wide age range, from children to the elderly. The clinical presentation is generally due to discovery of a testicular mass. Functional tumors are uncommon. The classification of testicular sex cord-stromal tumors is somewhat reminiscent of the classification of ovarian sex cord-stromal tumors, which are considerably more common. Thus, most pathologists are familiar with the terminology even though they may have little experience with these tumor types in the testis. We use the WHO classification, which is given below.

Sex Cord-Gonadal Stromal Tumors of the Testis
Leydig cell tumor
Malignant Leydig cell tumor

Sertoli cell tumor
    Lipid rich Sertoli cell tumor
    Sclerosing Sertoli cell tumor
    Large cell calcifying Sertoli cell tumor

Malignant Sertoli cell tumor

Granulosa cell tumor
    Juvenile granulosa cell tumor
    Adult type granulosa cell tumor

Tumors of fibroma/thecoma group
    Thecoma
    Fibroma

Unclassified sex cord-gonadal stromal tumor

Leydig Cell Tumor

The Leydig cell tumor is the most common testicular sex cord-stromal tumor. (Al-Agha and Axiotis 2007) There are two age peaks, one in children and one in adults, although the ages of adults with these tumors vary over a wide age range from 20 to 60 years. Children present with small tumors and almost always have isosexual precocity caused by androgen (usually testosterone) secreted by the tumor. About 10% have gynecomastia due to estrogen production by the tumor. Adults usually present with a testicular mass. About 30% have gynecomastia, which tends to be detected before the testicular tumor. A majority of adult

patients have abnormal serum levels of steroid hormones, with about a third of patients having increased serum androgens and a third, particularly those with gynecomastia, having elevated serum estrogen levels. (Suardi, Strada et al. 2009) Leydig cell tumors are more common in patients with cryptorchidism, testicular atrophy, and infertility. Some Leydig cell tumors occur in patients with germline fumarate hydratase mutations; (Carvajal-Carmona, Alam et al. 2006) these patients are also predisposed to hereditary leiomyomatosis and renal cell carcinoma.

Grossly, Leydig cell tumors are generally in the 2-5 cm range, with an average diameter of 3 cm. (Kim, Young et al. 1985) A few are larger, measuring up to 10 cm. On cut section, the testis contains a yellow, brown, or tan solid nodule. Many tumors have a characteristic yellow-brown color due to the presence of lipofuscin in the tumor cells. Hemorrhage and necrosis can be present. As would be anticipated, Leydig cell tumors are smaller in children. Leydig cell tumors are occasionally extratesticular. Gross features that are suggestive of malignancy include large size, an infiltrative edge, necrosis, and extratesticular extension. (Al-Agha and Axiotis 2007)

Microscopically, the tumor cells grow mainly in sheets, but other patterns include pseudoglandular, trabecular, and nodular growth. (Kim, Young et al. 1985) The nodules are separated by fibrous stroma. At low magnification, some tumors appear circumscribed, others push into the surrounding testicular parenchyma, and others infiltrate the surrounding testis. Rare patterns include growth in cords and trabeculae, formation of vague follicles, microcystic growth, (Billings, Roth et al. 1999) which can be confused with yolk sac tumor, and a spindle cell pattern, which can be either focal or be present extensively. (Ulbright, Srigley et al. 2002) In most tumors the cells are large and polygonal with abundant eosinophilic cytoplasm and round nuclei with prominent nucleoli. Some tumors contain large cells with abundant foamy pale cytoplasm and smaller nuclei resulting in an adrenal cortical like appearance, and in others the cells have round hyperchromatic nuclei and less abundant cytoplasm. The nuclei tend to be relatively uniform and mitotic figures are usually infrequent. Finely granular yellow brown lipofuscin pigment is present in the tumor cell cytoplasm in some cases. Lipofuscin has a red purple granular appearance in sections stained with a PAS stain. Crystalloids of Reinke are eosinophilic rod-shaped cytoplasmic structures that are the most definitive light microscopic marker of Leydig cell differentiation. Unfortunately, they can be identified in only about 40% of Leydig cell tumors. Rare Leydig cell tumors have clear cytoplasm, potentially leading to confusion with seminoma. Fat, calcifications, and osseous metaplasia sometimes present. (Ulbright, Srigley et al. 2002) Often, the fat appears to result from accumulation of lipid in the tumor cells.

Immunohistochemistry is useful in the diagnosis of Leydig cell tumors. Positive markers include inhibin, calretinin, and melan-A. (Busam, Iversen et al. 1998; Iczkowski, Bostwick et al. 1998; McCluggage, Shanks et al. 1998; Augusto, Leteurtre et al. 2002) We have had good luck staining Leydig cell tumors with steroidogenic factor-1. CD99 is positive, with staining of tumor cell membranes in about 2/3 of cases. Most Leydig cell tumors show positive staining for vimentin. Other staining reactions that have been reported include staining for chromogranin (>90%), synaptophysin (70%), S100 (8% in one study, 62% in another) and cytokeratin (~ 40%). (Iczkowski, Bostwick et al. 1998)

UCSF Immunostain Panel for Leydig Cell Tumor	
Stain	*Anticipated Result*
Inhibin	Positive, cytoplasmic
Steroidogenic factor-1	Positive, nuclear
Melan-A	Positive, cytoplasmic, granular
Cytokeratin cocktail	Negative (but 30-40% positive)
Epithelial Membrane Antigen	Negative

Malignant Leydig cell tumors are most common in older patients. (Cheville, Sebo et al. 1998) Tumors that occur in patients with gynecomastia are more likely to be benign. No clinically malignant Leydig cell tumors have occurred in prepuberal children, although one tumor in a 1-year-old boy appeared histologically malignant. (Drut, Wludarski et al. 2006) Pathologic features that are suspicious for malignancy include large tumor size (> 5cm), frequent mitotic figures (> 3/10 hpf), atypical mitotic figures, vascular space invasion, nuclear atypia, necrosis, invasive borders, and invasion of the rete testis or beyond. (Kim, Young et al. 1985; Cheville, Sebo et al. 1998) Clinicopathological studies based on consultation cases seem to have a higher percentage of malignant tumors than actually occur in practice. Several recent clinical series have found tumor related deaths to be uncommon (1 of 52 patients in one study; 0 of 37patients in another). (Di Tonno, Tavolini et al. 2009; Suardi, Strada et al. 2009) Testis sparing surgery appears safe and effective, provided that the diagnosis can be made at frozen section and the tumor is small with no gross or histologic features of suggestive of malignancy. (Giannarini, Mogorovich et al. 2007; Suardi, Strada et al. 2009) No effective chemotherapy protocols have been identified nor does radiation therapy appear helpful. It is unclear whether retroperitoneal lymph node dissection is beneficial.

Features Suggestive of Malignancy in Leydig Cell Tumors
Old age (never malignant in young children)
Large size, tumor diameter > 5 cm
Mitotic activity (> 3 mf per 10 hpf)
Atypical mitotic figures
Lymphovascular space invasion
Nuclear atypia
Necrosis
Invasive growth

The differential diagnosis of a Leydig cell tumor includes a number of non-neoplastic hyperplasias as well as several types of neoplasms.

-*Leydig cell hyperplasia, nodular type*. Hyperplastic Leydig cell nodules exhibit non-destructive growth of Leydig cells in an interstitial location between the tubules. The nodules tend to be multiple, and they can be bilateral. They are usually small (< 0.5 cm). Leydig cell hyperplasia can occur in patients with elevated gonadotropin levels.

-Testicular tumor of the adrenogenital syndrome (TTAGS). Patients with adrenogenital syndrome, usually of the salt loosing type caused by a 21-hydroxylase deficiency, or Nelson's syndrome (ACTH secreting pituitary adenoma in patients treated by bilateral adrenalectomy for Cushing's syndrome) can have multifocal and bilateral nodules that can mimic a Leydig cell tumor. (Rutgers, Young et al. 1988) TTAGS are hyperplastic nodules caused by elevated levels of ACTH. Often, the history is known, which facilitates the correct diagnosis, but occasionally the testicular tumors are discovered prior to diagnosis of the adrenogenital syndrome. Grossly, the tumors can be large, measuring up to 5-10 cm, or they can be small and impalpable. Small tumors are often centered in the hilum of the testis. In general, tumors in children are small and those that are detected in older patients are larger. The cut surfaces are brown with confluent nodules separated by broad bands of fibrous tissue. The tumor cells are large and polygonal with uniform round nuclei with nucleoli and abundant eosinophilic or pale cytoplasm. Some nodules contain cells with clear vacuolated cytoplasm. The cytoplasm contains lipofuscin but no Reinke crystalloids are present. Fibrous bands that are generally broader and more extensive than occur in Leydig cell tumors separate nests of cells. Sometimes, when the nodules are hilar, rete tubules are present between them. These "tumors" are not true neoplasms, but nodular hyperplasias that regress with treatment that lowers adrenocorticotrophin levels.

-Large cell calcifying Sertoli cell tumor. Many examples of this tumor occur in patients with the Carney syndrome, as discussed below. These tumors can be confused with Leydig cell tumors because the tumor cells are polygonal and have abundant eosinophilic cytoplasm. No Reinke crystalloids are identified. This type of Sertoli cell tumor characteristically contains calcifications, can grow in tubules, and has a more myxoid stroma that often contains neutrophils.

-Seminoma. A Leydig cell tumor with clear cytoplasm can be confused with a seminoma, but in the case of the Leydig cell tumor the clear cytoplasm due to the presence of lipids, not glycogen. Findings that are present in association with seminoma, but not a Leydig cell tumor, include intratubular germ cell neoplasia, lymphocytes, typically in fibrous septae and sometimes forming germinal centers, and granulomas. Of course, the immunohistochemical features of a seminoma are totally different than those of a Leydig cell tumor.

Sertoli Cell Tumor

A variety of types of Sertoli cell tumor have been described, with interesting histologic patterns or unusual clinical associations, or both. Sertoli cell tumors, nos are the most common, and a tumor designated simply as a "Sertoli cell tumor" is generally taken to be a Sertoli cell tumor, nos.

Sertoli Cell Tumors of the Testis
Sertoli cell tumor, nos
Sclerosing Sertoli cell tumor
Large cell calcifying Sertoli cell tumor
Sertoli cell tumor associated with Peutz-Jeghers syndrome

Sertoli cell tumors occur in patients of all ages. About a third of them occur in children less than 10 years old, (Harms and Kock 1997) but they are most common in middle-aged men. The average age is about 45. (Young, Koelliker et al. 1998) The typical presentation is with a slowly enlarging testicular mass. They are almost always unilateral. Most tumors are nonfunctional. Tumors that secret estrogens are unusual, but these can cause gynecomastia or impotence.

Gynecomastia in Sertoli Cell Tumors	
Sertoli cell tumor, nos	Rare
Sclerosing Sertoli cell tumor	Never
Large cell calcifying Sertoli cell tumor	Rare

Grossly, Sertoli cell tumors are solid gray, white or tan masses, usually less than 4 cm in diameter. Cystic change can be present.

Microscopically, a nodular pattern is often prominent at low magnification, with the nodules separated by broad bands of fibrous tissue. A variety of growth patterns are recognized, including growth of tumor cells in sheets, nests, trabeculae and cords. However, these patterns are not specific and for a definitive diagnosis tubules must be identified. The tubules can be solid or hollow and rarely elongated branching rete like tubules lined by cuboidal cells are present. The tubules are often poorly formed and sometimes it requires some imagination to recognize them. The background tends to be fibrous but it can be hyalinized or myxoid. The tumor cells are cuboidal to columnar and have scant to moderate pale or clear cytoplasm. Some tumors are composed mainly of polygonal cells with abundant eosinophilic cytoplasm. Zones composed of spindle cells are occasionally present in a Sertoli cell tumor. A variant with abundant clear foamy cytoplasm, the lipid rich variant, has been described. Cytoplasmic vacuoles are common and prominent cytoplasmic vacuolization can result in a microcystic appearance. The tumor cell nuclei are uniform and round to oval with small nucleoli.

Immunohistochemical stains for inhibin, cytokeratin, and vimentin are positive. (Iczkowski, Bostwick et al. 1998; McCluggage, Shanks et al. 1998; Kommoss, Oliva et al. 2000; Kato, Fukase et al. 2001; Comperat, Tissier et al. 2004) About half stain for calretinin. Other sex cord-stromal markers, such as WT-1, CD99 and melan-A can be positive. Many Sertoli cell tumors show positive staining for S100. Chromogranin and synaptophysin have been reported as positive in some studies. Sertoli cells are usually negative for EMA, but malignant Sertoli cell tumors can be positive.

About 10% of Sertoli cell tumors are malignant. Malignant Sertoli cell tumors occur in children as well as in adults. Gynecomastia is more common in malignant cases. Malignant Sertoli cell tumors do not respond to chemotherapy or radiotherapy, so surgery is the mainstay of treatment and retroperitoneal lymph node dissection is generally advised. Metastatic spread is to the retroperitoneal lymph nodes and lungs. Pathologic features that suggest malignancy include marked nuclear atypia and pleomorphism, frequent mitotic figures (> 5mf/10hpf), vascular invasion, necrosis, large size (>5 cm), and predominance of a diffuse growth pattern.

Several benign pseudotumors must be considered in the differential diagnosis, along with other neoplasms. The differential diagnosis is mainly with the following:

-*Hamartomatous Sertoli cell nodules of the androgen insensitivity syndrome*. Patients with the AIS ("testicular feminization") have multiple testicular hamartomatous nodules composed of tubules lined by Sertoli cells. Leydig cells are often present in the stroma between the tubules, in contrast to Sertoli cell tumors, where Leydig cells are pushed aside. About 25% of patients with the AIS develop multifocal bilateral Sertoli cell adenomas composed of pure proliferations of Sertoli cells lining tubules. It is unclear whether these are hyperplastic nodules, or autonomous neoplastic nodules but in any event malignant behavior has never been observed. The adenomas often contain eosinophilic waxy basement membrane deposits.

-*Small Sertoli cell nodules*. Small nodules of Sertoli cells are a common incidental microscopic finding common in orchiectomy specimens from cryptorchid patients. These nodules are not grossly visible, in contrast to Sertoli cell tumors, which are usually > 1 cm in diameter. The nodules often contain central accumulations of basement membrane material.

-*Seminoma*. In some malignant Sertoli cell tumors the tumor cells have clear cytoplasm and grow in sheets. Lymphocytes are scattered among the tumor cells, but plasma cells, which are uncommon in seminoma, are often numerous as well. This results in a histologic picture that can lead to a misdiagnosis as seminoma. (Henley, Young et al. 2002; Ulbright 2008) Unlike seminoma cells, the Sertoli cells often contain cytoplasmic vacuoles, have smaller round nuclei, and do not have conspicuous nucleoli. Mitotic figures are usually more numerous in seminoma. The presence of granulomas or intratubular germ cell neoplasia would favor a diagnosis of seminoma. The immunohistochemical findings permit a clear distinction between Sertoli cell tumor and seminoma. Many seminoma-like Sertoli cell tumors occur in older men at an age when seminoma is uncommon (> 55 years old).

Variants of Sertoli Cell Tumor

Several variants of Sertoli cell tumor have been described. These have distinctive histologic or clinical features, or both. The most important of these are sclerosing Sertoli cell tumor, large cell calcifying Sertoli cell tumor and Sertoli cell tumors in patients with the Peutz-Jeghers syndrome.

Sclerosing Sertoli Cell Tumor

Sclerosing Sertoli cell tumors occur predominantly in young men with an average age of 35 years. (Zukerberg, Young et al. 1991) They either present as a painless slowly enlarging testicular mass without any associated hormonal symptoms or the tumor is incidental finding.Grossly, sclerosing Sertoli cell tumors are small hard solid nodules with a white to yellow tan cut surface. Most are < 1.5 cm in diameter, although rare larger tumors have been reported. Microscopically, the tumor cells grow in cords, solid or hollow tubules, or as nests of cells. The key finding in this variant of Sertoli cell tumor is the densely collagenous background stroma that dominates the histologic picture and compresses the tubules, prompting the name "sclerosing" Sertoli cell tumor. (Zukerberg, Young et al. 1991) The sclerosis should be present throughout the tumor, not just focally, for classification as a sclerosing Sertoli cell tumor. The tumor cells nuclei vary from large and vesicular to small and hyperchromatic. They are usually columnar or cuboidal and have pale, sometimes

vacuolated cytoplasm. Mitotic activity and nuclear atypia have only een reported in one case. All reported sclerosing Sertoli cell tumors have had a benign evolution.

Large Cell Calcifying Sertoli Cell Tumor

Patients with this type of Sertoli cell tumor tend to be young, with an average age of 16, although tumors occur over a wide age range from children to older adults. (Proppe and Scully 1980) The usual presentation is with a slowly enlarging painless testicular mass. Hormones may be produced by the tumor or by hyperplastic Leydig cells in the surrounding testis, and some patients accordingly present with endocrine associated symptoms such as gynecomastia or isosexual precocity. About 40% of large cell calcifying Sertoli cell tumors occur in patients with Carney's syndrome or another genetic syndrome such as Peutz-Jeghers syndrome. (Kratzer, Ulbright et al. 1997) Tumors in Carney's patients are small, bilateral and multifocal and they are usually detected in childhood or adolescence. Other findings associated with the Carney syndrome include lentigines of the face, myxomas of the heart, skin and soft tissue, myxoid fibroadenomas of the breast, blue nevi of skin, pigmented nodules of the adrenal cortex with Cushing's syndrome, human growth hormone producing adenomas of pituitary and psammomatous melanotic schwannomas. Pathologists should always bring up the possibility that the patient might have the Carney syndrome if a large cell calcifying Sertoli cell tumor is diagnosed, particularly if it is bilateral and multifocal. Grossly, the tumor is tan or yellow and contains gritty areas of calcification. Most measure less than 4 cm in diameter. Large cell calcifying Sertoli cell tumors are unusual in that they can be multifocal and about 40% are bilateral.

Microscopically, the tumor consists of nests, cords, trabeculae and solid tubules of polygonal cells with abundant eosinophilic cytoplasm. The tumor cell nuclei are round and vesicular with prominent nucleoli. Mitotic figures are rare. Intratubular growth and calcifications are common. The tumor cells grow in myxoid to collagenous stroma that is calcified or ossified in about half the cases. A neutrophilic stromal infiltrate is characteristic. The tumor cells stain for vimentin and are inhibin and melan-A positive. (Petersson, Bulimbasic et al. 2010) They are usually cytokeratin negative although infrequently there is minimal focal staining. (Kratzer, Ulbright et al. 1997) The tumor cells are EMA negative. Given the appearance of the tumor cells, it is worth noting that they usually stain for S100, which could potentially lead to confusion with metastatic melanoma.

The differential diagnosis includes Leydig cell tumor because of the polygonal cell shape and abundant eosinophilic cytoplasm, but Leydig cell tumors generally lack a neutrophilic infiltrate and calcifications, do not exhibit tubular growth and do not grow within tubules. Large cell calcifiying Sertoli cell tumors do not contain crystalloids of Reinke or lipofuscin.

Malignant large cell calcifying Sertoli cell tumors are rare, but some have been reported. (Kratzer, Ulbright et al. 1997) Patients with malignant tumors are older than those with malignant tumors (average age 39 vs 17) and malignant tumors generally do not occur in patients with the Carney syndrome. Features suggestive of malignancy include large size (>4 cm), extratesticular growth, tumor cell necrosis, high-grade nuclear atypia, frequent mitotic figures (mitotic rate > 3 mf/10 hpf) and vascular invasion. It has been suggested that if one of these features is present the possibility of malignancy should be mentioned, and if two or more are present the tumor should be classified as malignant. (Kratzer, Ulbright et al. 1997) Invasion of the rete testis has been noted in a few benign cases. (Plata, Algaba et al.

1995) Occasional tumors with none of these features, such as one with minimal atypia and no mitotic activity but with invasion of the rete testis, prove to be malignant. (De Raeve, Schoonooghe et al. 2003)

Sertoli Cell Proliferations in Peutz Jeghers Syndrome

Patients with the Peutz-Jeghers syndrome develop multifocal bilateral intratubular proliferations of Sertoli cells that occur in lobular clusters through out the parenchyma. (Venara, Rey et al. 2001; Ulbright, Amin et al. 2007) Most patients are children; they all have gynecomastia and some have isosexual precocity depending on the hormone or hormones produced. Many patients have other features of Peutz-Jeghers syndrome, such as pigmented macules around the mouth and on the lips. The testes are generally bilaterally enlarged with echogenic foci on ultrasound examination, but a palpable mass is not present; rare patients have unilateral testicular enlargement. The diagnosis is generally made by testicular biopsy, usually performed bilaterally. The involved tubules are expanded and contain cells similar to those in a large cell calcifying Sertoli tumor. They are polygonal with abundant eosinophilic cytoplasm. There is abundant eosinophilic hyalinized basement membrane material in the expanded tubules. Sometimes the growth pattern is annular and with the prominent hyaline material it is reminiscent of the sex cord tumor with annular tubules (SCTAT) that occurs in the ovaries of women with the Peutz-Jeghers syndrome. Usually, calcifications are not present. In most cases the proliferation is entirely intratubular, but in a minority of patients an invasive Sertoli cell tumor is also present. (Young, Gooneratne et al. 1995; Venara, Rey et al. 2001) The invasive tumors are usually small and their classification is problematic. Some resemble large cell calcifying Sertoli cell tumors but they lack calcifications and do not have the prominent fibromyxoid stroma with neutrophils. Others have a more tubular pattern. Followup has not revealed progression in patients who have only intratubular proliferations at diagnosis, so the nature of these proliferations remains unsettled. Ulbright et al favor interpreting them as intratubular neoplasms because of the occasional association with an invasive neoplasm.

Granulosa Cell Tumor

Granulosa cell tumors are rare types of testicular tumors. There are two variants, similar to the situation in the ovary. One type occurs mainly in adults, and is termed the adult type granulosa cell tumor. The other type occurs predominantly in young children, and is termed the juvenile type of granulosa cell tumor.

Adult Granulosa Cell Tumor

Adult type granulosa cell tumors are very rare. (Nistal, L†zaro et al. 1992; Jimenez-Quintero, Ro et al. 1993) In the only series reported, 7 granulosa cell tumors were found in a review of 52 sex cord stromal tumors at MD Anderson. (Jimenez-Quintero, Ro et al. 1993) Six cases were pathology consultations and one was a patient treated at MD Anderson. They occur over a wide age range, from 16-76 years. The average age is in the mid 40's. The presentation is with a painless testicular mass. A significant number of tumors have been asymptomatic and detected during routine physical examinations. Many tumors are nonfunctional, but others secrete estrogen and cause gynecomastia.

Grossly, adult type granulosa cell tumors can be solid, cystic, or solid and cystic. They form well-circumscribed nodules with cut surfaces that are yellow to gray. The average size is about 5 cm.

The same microscopic patterns that are seen in ovarian granulosa cell tumors occur in testicular granulosa cell tumors. These include microfollicular, trabecular, gyriform, insular, and diffuse patterns of growth. The diffuse pattern is the most common one. The tumor cells have scant pale cytoplasm. The nuclei are pale and round to oval with small nucleoli and, sometimes, nuclear grooves. Mitotic figures are usually uncommon, but they are occasionally numerous and readily identified.

Granulosa cell tumors of the testis show positive immunohistochemical staining for inhibin, vimentin, and, in some tumors, cytokeratin. Staining for EMA is negative.

Most of the reported cases have been clinically benign. The largest series included only seven patients, but 2 of the 5 patients included in that series developed metastases, (Jimenez-Quintero, Ro et al. 1993) and other patients with malignant tumors have been reported. The diagnosis in some reported cases is questionable; for example, Hammerich et al reported a tumor as a granulosa cell tumor, but their illustrations show a tumor that contains closed and open tubules, more suggestive of a Sertoli cell tumor. (Hammerich, Hille et al. 2008) Features that are worrisome for malignancy include large tumor size, vascular invasion, hemorrhage, and necrosis.

Juvenile Granulosa Cell Tumor

Juvenile granulosa cell tumors of the testis occur almost exclusively in young children. In the Kiel pediatric tumor registry sex cord-stromal tumors accounted for 17.7% of all testicular tumors, with juvenile granulosa cell tumors constituting 31.4% of the total. (Harms and Kock 1997) A majority of these tumors are diagnosed during the first days or weeks of life, (Lawrence, Young et al. 1985) and presumably are congenital tumors. More than 95% are diagnosed before the patient has reached the age of 1 year. As might be anticipated, some cases are diagnosed antenatally. (Peterson and Skoog 2008) Almost all patients present with a painless scrotal mass, but a few present because of testicular torsion. (Nistal, Redondo et al. 1988) A few tumors have been reported to occur in undescended testicles. Hormonal symptoms almost never occur. Most patients have a normal 46XY karyotype.

On gross exam, the testis contains a solid to cystic gray or yellow nodule that usually occupies most of the testis, often leaving only a thin rim of normal testicular parenchyma. The cut surface can be nodular or microcystic, with small cysts only 1-2 mm in diameter, or larger cysts may be present. The tumor size ranges from less than a cm to about 5 cm, with an average diameter of about 2 cm. (Lawrence, Young et al. 1985; Harms and Kock 1997)

Microscopically, solid cellular areas are intermixed with follicle like structures filled with mucoid material. The follicle contents are often basophilic and stain lightly with mucicarmine. The follicles tend to be large and somewhat irregular, and can be termed macrofollicles. The follicles are lined by several layers of stratified tumor cells and surrounded by a spindle cell stroma or by neoplastic granulosa cells. Solid areas may contain abundant hyalinized stroma. The tumor cells have abundant pale to eosinophilic cytoplasm and in some tumors they are focally or diffusely luteinized. The nuclei are round and hyperchromatic and often contain conspicuous nucleoli. Mitotic figures are generally readily

identified and they can be numerous. The degree of atypia is typically less than is seen in ovarian juvenile granulosa cell tumors.

Immunohistochemical studies of these tumors are limited, but they have been shown to be positive for inhibin, vimentin and CD99 and to stain focally for cytokeratin. As has been observed in ovarian granulosa cell tumors, the cells can stain for S100 and SMA. (Alexiev, Alaish et al. 2007) The results of staining for other antigens have not been reported, but positive staining for sex cord-stromal markers such as calretinin and steroidogenic factor-1 is likely to be present.

Malignant behavior has not reported. Follow-up studies are limited, but all patients have been well after orchiectomy or enucleation. In view of the favorable outcome, fertility sparing enucleation has been advocated in patients who have a normal serum AFP (presumably excluding yolk sac tumor). (Shukla, Huff et al. 2004)

The histogenesis is controversial. In one series of 14 juvenile granulosa cell tumors one example showed intratubular growth adjacent to the main tumor mass. This has led to speculation that the tumors may be derived from Sertoli cells.

The differential diagnosis includes other types of sex cord stromal tumors, but the main differential diagnosis is with yolk sac tumor. Yolk sac tumor exhibits a number of distinctive growth patterns that are not seen in juvenile granulosa cell tumor, so adequate histologic study usually resolves the issue. In addition, there are significant immunohistochemical differences between the two, with juvenile granulosa cell tumor being positive for inhibin, calretinin, and steroidogenic factor-1, and yolk sac tumor showing positive staining for cytokeratin, alpha-fetoprotein, SALL4, and glypican-3.

Fibroma Thecoma Group

Tumors that resemble fibromas or thecomas of the ovary are extremely rare. (Jones, Young et al. 1997) They are generally small and circumscribed with a yellow or white cut surface. Microscopically, they consist of bundles of bland spindle cells with oval nuclei and scanty cytoplasm. A variable amount of collagen is present in the background. Several cellular fibromas, similar in appearance to the corresponding ovarian tumors, have been reported. Several tumors with minor aggregates of sex cord elements have been reported. (De Pinieux, Glaser et al. 1999) The presence of more than a minor amount of sex cord cells excludes a tumor from the fibroma category, and requires its placement in the mixed or unclassified category, discussed below, since such tumors have metastatic potential that is lacking in fibroma.

Mixed and Unclassified Sex Cord Stromal Tumors

This category contains tumors that cannot be accurately placed into one of the defined categories of sex cord stromal tumors. They usually present as a painless testicular mass. About a third of these tumors occur in children, in whom 2/3 of sex cord stromal tumors fall into this category. About 15% of patients have gynecomastia.

Grossly, they are gray, tan or yellow solid nodules. Microscopically, they often contain a mixture of sex cord and stromal elements. A combination of epithelioid and spindled tumor cells is typical, although in some tumors spindled cells predominate. (Renshaw, Gordon et al. 1997; Magro, Gurrera et al. 2007) In some tumors there are focal Sertoli tubules or aggregates of granulosa like cells, but the tumor does not fit well into either category. In tumors that contain a mixture of well defined types of sex cord and stromal

elements, all should be listed in the report; the behavior is likely to be determined by a combination of the percentage of each type and its malignant potential.

These tumors have all been benign in children less than 10 years of age but about 20% of those that occur in older patients are malignant. Worrisome findings include cellular atypia and pleomorphism, a high mitotic rate, necrosis, vascular invasion, an invasive margin and large tumor size.

<div align="center">References</div>

Al-Agha, O. M. and C. A. Axiotis (2007). "An in-depth look at Leydig cell tumor of the testis." Arch Pathol Lab Med **131**(2): 311-317.

Alexiev, B. A., S. M. Alaish, et al. (2007). "Testicular juvenile granulosa cell tumor in a newborn: case report and review of the literature." International Journal of Surgical Pathology **15**(3): 321-325.

Augusto, D., E. Leteurtre, et al. (2002). "Calretinin: a valuable marker of normal and neoplastic Leydig cells of the testis." Applied Immunohistochemistry & Molecular Morphology **10**(2): 159-162.

Billings, S. D., L. M. Roth, et al. (1999). "Microcystic leydig cell tumors mimicking yolk sac tumor - A report of four cases." American Journal of Surgical Pathology **23**(5): 546-551.

Busam, K. J., K. Iversen, et al. (1998). "Immunoreactivity for A103, an antibody to Melan-A (MART-1), in adrenocortical and other steroid tumors." Am.J Surg.Pathol **22**(1): 57-63.

Carvajal-Carmona, L. G., N. A. Alam, et al. (2006). "Adult leydig cell tumors of the testis caused by germline fumarate hydratase mutations." J Clin Endocrinol Metab **91**(8): 3071-3075.

Cheville, J. C., T. J. Sebo, et al. (1998). "Leydig cell tumor of the testis - A clinicopathologic, DNA content, and MIB-1 comparison of nonmetastasizing and metastasizing tumors." American Journal of Surgical Pathology **22**: 1361-1367.

Comperat, E., F. Tissier, et al. (2004). "Non-Leydig sex-cord tumors of the testis. The place of immunohistochemistry in diagnosis and prognosis. A study of twenty cases." Virchows Archiv: an International Journal of Pathology **444**(6): 567-571.

De Pinieux, G., C. Glaser, et al. (1999). "Testicular fibroma of gonadal stromal origin with minor sex cord elements - Clinicopathologic and immunohistochemical study of 2 cases." Archives of Pathology and Laboratory Medicine **123**(5): 391-394.

De Raeve, H., P. Schoonooghe, et al. (2003). "Malignant large cell calcifying Sertoli cell tumor of the testis." Pathol Res Pract **199**(2): 113-117.

Di Tonno, F., I. M. Tavolini, et al. (2009). "Lessons from 52 patients with leydig cell tumor of the testis: the GUONE (North-Eastern Uro-Oncological Group, Italy) experience." Urol Int **82**(2): 152-157.

Drut, R., S. Wludarski, et al. (2006). "Leydig cell tumor of the testis with histological and immunohistochemical features of malignancy in a 1-year-old boy with isosexual pseudoprecocity." International Journal of Surgical Pathology **14**(4): 344-348.

Giannarini, G., A. Mogorovich, et al. (2007). "Long-term followup after elective testis sparing surgery for Leydig cell tumors: a single center experience." J Urol **178**(3 Pt 1): 872-876; quiz 1129.

Hammerich, K. H., S. Hille, et al. (2008). "Malignant advanced granulosa cell tumor of the adult testis: case report and review of the literature." Human Pathology **39**(5): 701-709.

Harms, D. and L. R. Kock (1997). "Testicular juvenile granulosa cell and Sertoli cell tumours: A clinicopathological study of 29 cases from the Kiel Paediatric Tumour Registry." Virchows Archiv: an International Journal of Pathology **430**(4): 301-309.

Henley, J. D., R. H. Young, et al. (2002). "Malignant Sertoli cell tumors of the testis: a study of 13 examples of a neoplasm frequently misinterpreted as seminoma." Am J Surg Pathol **26**(5): 541-550.

Iczkowski, K. A., D. G. Bostwick, et al. (1998). "Inhibin A is a sensitive and specific marker for testicular sex cord- stromal tumors." Modern Pathology **11**(8): 774-779.

Jimenez-Quintero, L. P., J. Y. Ro, et al. (1993). "Granulosa cell tumor of the adult testis: A clinicopathologic study of seven cases and a review of the literature." Human Pathology **24**: 1120-1126.

Jones, M. A., R. H. Young, et al. (1997). "Benign fibromatous tumors of the testis and paratesticular region: A report of 9 cases with a proposed classification of fibromatous tumors and tumor-like lesions." American Journal of Surgical Pathology **21**(3): 296-305.

Kato, N., M. Fukase, et al. (2001). "Sertoli-stromal cell tumor of the ovary: Immunohistochemical, ultrastructural, and genetic studies." Human Pathology **32**(8): 796-802.

Kim, I., R. H. Young, et al. (1985). "Leydig cell tumors of the testis. A clinicopathological analysis of 40 cases and review of the literature." American Journal of Surgical Pathology **9**(3): 177-192.

Kommoss, F., E. Oliva, et al. (2000). "Inhibin-alpha, CD99, HEA125, PLAP and chromogranin immunoreactivity in testicular neoplasms and the androgen insensitivity syndrome." Human Pathology **31**(9): 1055-1061.

Kratzer, S. S., T. M. Ulbright, et al. (1997). "Large cell calcifying Sertoli cell tumor of the testis: contrasting features of six malignant and six benign tumors and a review of the literature." American Journal of Surgical Pathology **21**(11): 1271-1280.

Lawrence, W. D., R. H. Young, et al. (1985). "Juvenile granulosa cell tumor of the infantile testis. A report of 14 cases." Am J Surg Pathol **9**(2): 87-94.

Magro, G., A. Gurrera, et al. (2007). "Incompletely differentiated (unclassified) sex cord/gonadal stromal tumor of the testis with a "pure" spindle cell component: report of a case with diagnostic and histogenetic considerations." Pathol Res Pract **203**(10): 759-762.

McCluggage, W. G., J. H. Shanks, et al. (1998). "Immunohistochemical study of testicular sex cord stromal tumors, including staining with anti-inhibin antibody." American Journal of Surgical Pathology **22**(5): 615-619.

Nistal, M., R. L†zaro, et al. (1992). "Testicular granulosa cell tumor of the adult type." Archives of Pathology and Laboratory Medicine **116**: 284-287.

Nistal, M., E. Redondo, et al. (1988). "Juvenile granulosa cell tumor of the testis." Arch Pathol Lab Med **112**(11): 1129-1132.

Peterson, C. and S. Skoog (2008). "Prenatal diagnosis of juvenile granulosa cell tumor of the testis." J Pediatr Urol **4**(6): 472-474.

Petersson, F., S. Bulimbasic, et al. (2010). "Large cell calcifying Sertoli cell tumor: a clinicopathologic study of 1 malignant and 3 benign tumors using histomorphology, immunohistochemistry, ultrastructure, comparative

genomic hybridization, and polymerase chain reaction analysis of the PRKAR1A gene." <u>Hum Pathol</u> **41**(4): 552-559.

Plata, C., F. Algaba, et al. (1995). "Large cell calcifying Sertoli cell tumour of the testis." <u>Histopathology</u> **26**: 255-259.

Proppe, K. H. and R. E. Scully (1980). "Large-cell calcifying Sertoli cell tumor of the testis." <u>Am J Clin Pathol</u> **74**(5): 607-619.

Renshaw, A. A., M. Gordon, et al. (1997). "Immunohistochemistry of unclassified sex cord-stromal tumors of the testis with a predominance of spindle cells." <u>Modern Pathology</u> **10**: 693-700.

Rutgers, J. L., R. H. Young, et al. (1988). "The testicular "tumor" of the adrenogenital syndrome. A report of six cases and review of the literature on testicular masses in patients with adrenocortical disorders." <u>Am J Surg Pathol</u> **12**(7): 503-513.

Shukla, A. R., D. S. Huff, et al. (2004). "Juvenile granulosa cell tumor of the testis:: contemporary clinical management and pathological diagnosis." <u>Journal of Urology</u> **171**(5): 1900-1902.

Suardi, N., E. Strada, et al. (2009). "Leydig cell tumour of the testis: presentation, therapy, long-term follow-up and the role of organ-sparing surgery in a single-institution experience." <u>BJU Int</u> **103**(2): 197-200.

Ulbright, T. M. (2008). "The most common, clinically significant misdiagnoses in testicular tumor pathology, and how to avoid them." <u>Advances in Anatomic Pathology</u> **15**(1): 18-27.

Ulbright, T. M., M. B. Amin, et al. (2007). "Intratubular Large Cell Hyalinizing Sertoli Cell Neoplasia of the Testis: A Report of 8 Cases of a Distinctive Lesion of the Peutz-Jeghers Syndrome." <u>American Journal of Surgical Pathology</u> **31**(6): 827-835.

Ulbright, T. M., J. R. Srigley, et al. (2002). "Leydig cell tumors of the testis with unusual features - Adipose differentiation, calcification with ossification, and spindle-shaped tumor cells." <u>American Journal of Surgical Pathology</u> **26**(11): 1424-1433.

Ulbright, T. M., J. R. Srigley, et al. (2002). "Leydig cell tumors of the testis with unusual features: adipose differentiation, calcification with ossification, and spindle-shaped tumor cells." <u>Am J Surg Pathol</u> **26**(11): 1424-1433.

Venara, M., R. Rey, et al. (2001). "Sertoli cell proliferations of the infantile testis - An intratubular form of Sertoli cell tumor?" <u>American Journal of Surgical Pathology</u> **25**(10): 1237-1244.

Young, R. H., D. D. Koelliker, et al. (1998). "Sertoli cell tumors of the testis, not other-wise specified - A clinicopathologic analysis of 60 cases." <u>American Journal of Surgical Pathology</u> **22**(6): 709-721.

Young, S., S. Gooneratne, et al. (1995). "Feminizing Sertoli cell tumors in boys with Peutz-Jeghers syndrome." <u>American Journal of Surgical Pathology</u> **19**: 50-58.

Zukerberg, L. R., R. H. Young, et al. (1991). "Sclerosing Sertoli cell tumor of the testis. A report of 10 cases." <u>American Journal of Surgical Pathology</u> **15**(9): 829-834.