Leydig Cells and Sertoli Cells — Sex Cord-Stromal Tumor of the Testis

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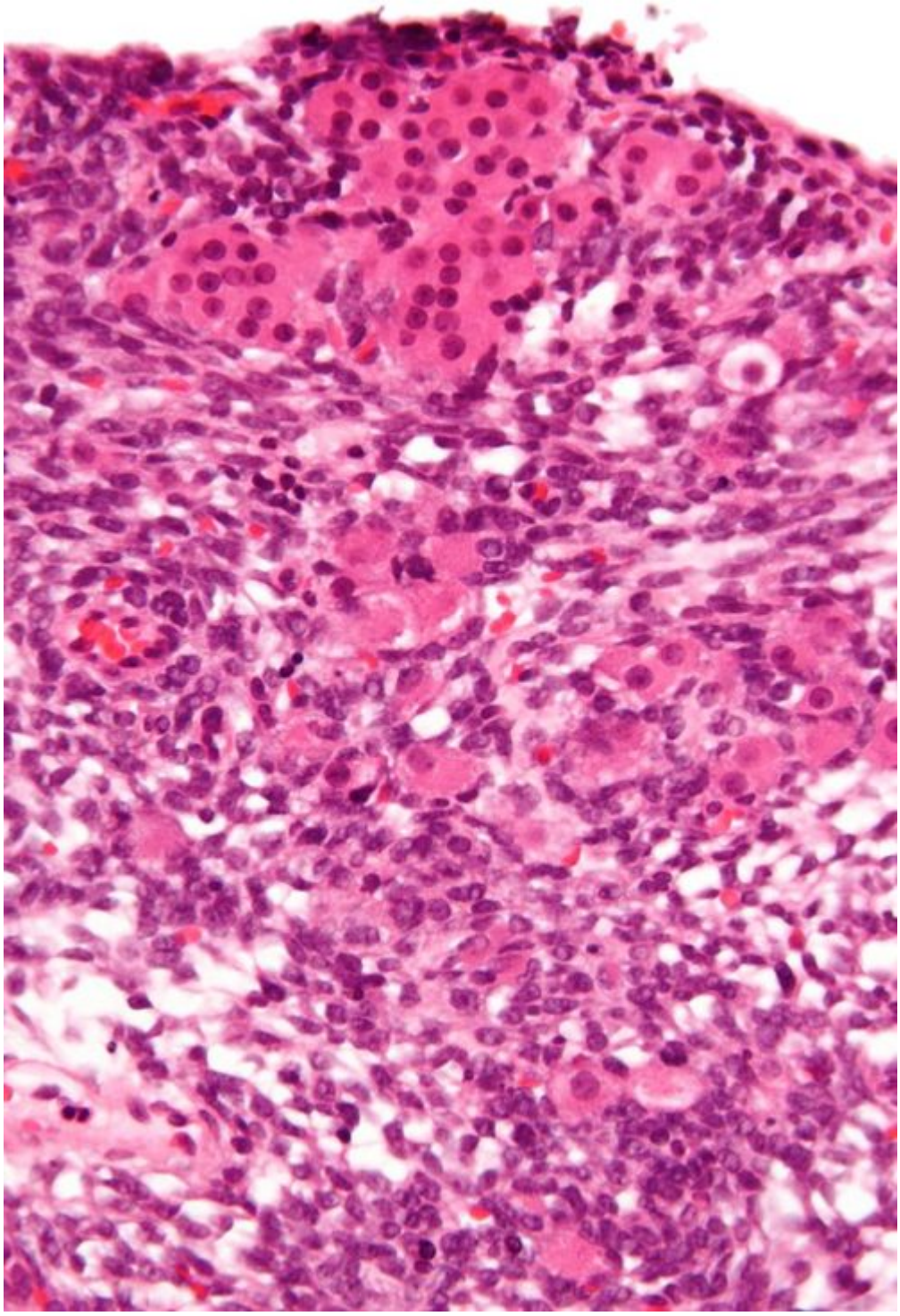
Sex cord stromal tumors of the testis can originate from either Leydig cells or Sertoli cells. Leydig cells tumors are responsible for 70%. These testicular tumors are known to cause estrogen excess production and a low testosterone-estrogen ratio. Alpha-fetoprotein, human chorionic gonadotropin and lactate dehydrogenase levels are normal in this type of tumors. Ultrasonography confirms the diagnosis of a testicular mass, while biopsy and histologic examination confirm the diagnosis of either Leydig cells or Sertoli cells tumor. Treatment of choice is radical inguinal orchiectomy.



Definition of Sex Cord-Stromal Tumors of the Testis

Sex cord-stromal tumors of the testis are a rare form of **testicular tumors** that originate from Leydig cells or Sertoli cells.Thus, they include Leydig cell tumors, Sertoli cell tumors and granulosa cell tumors. The Leydig cell tumors are derived from normal Leydig cells that produce testosterone and are in the interstitium. While Sertoli cell tumors are located within the seminiferous tubules. Sertoli cell tumors can be of the:

1. Sclerosing Sertoli cell tumor

2. Large cell calcifying Sertoli cell tumor

Granulosa cells are not native to the testis.Approximately 10 % of sex cord-stromal tumors are thought to be malignant.

Epidemiology of Sex Cord-Stromal Tumors of the Testis

Sex cord-stromal tumors of the testis can be considered as the **rarest form of testicular tumors**. The most common form of testicular cancer is **germ cell tumors**.

The most common type of sex cord-stromal tumors is **Leydig cell tumors**, which accounts for more than 70 % of the cases of sex cord-stromal tumors of the testis and only 3 % of all testicular neoplasms while Leydig cell tumors form a minority of the sex cord stromal tumors and less than 1 % of all testicular tumors.

Only 10 % of sex cord-stromal tumors are truly malignant. However, up to 20 % of the patients with sex cord-stromal tumors present with **distant metastasis** at the time of presentation.

Like germ cell tumors, sex cord-stromal tumors are usually seen in young adults. Leydig cell tumors are most common in **prepubertal boys** and in **middle-aged men**. Sex cord-stromal tumors are not related to **cryptorchidism**.

Sertoli cell tumors are less common than Leydig cell tumors and are usually seen in **middle-aged men** and rarely in men younger than 20 years.

Etiology and Pathophysiology of Sex Cord-Stromal Tumors of the Testis

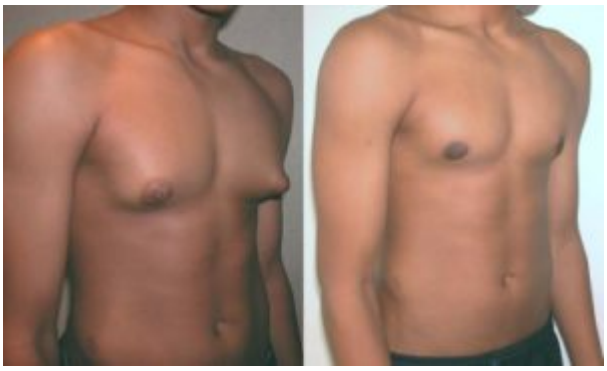


Image: “Adolescent with Gynecomastia.” by David Andrew Copeland, Dr. Mordcai Blau www.gynecomastia-md.com – Own work. License: CC BY-SA 3.0

Unlike germ cell tumors of the testis, risk factors for sex cord-stromal tumors are rarely identified in the patient. Leydig and Sertoli cells are functionally active and patients with these tumors will have an **excess of either testosterone or estrogen**, which can result in precocious puberty. Because of the excess of estrogen production, patients can also develop **gynecomastia**.

Histopathologic examination of Leydig cell tumors revealed **DNA ploidy** which has been linked to the degree of malignancy. Sertoli cells might be mistaken for **seminomas**. The

cells usually are arranged in cord-like structures, contain **Call-Exner bodies**, and express **vimentin**, **cytokeratin**, **inhibin** and **protein S100**.

Clinical Presentation of Sex Cord-Stromal Tumors of the Testis

Patients with sex cord-stromal tumors of the testis usually present with a **testicular mass,** the same as other testicular tumors, or with **secondary symptoms to endocrinological disturbance** such as **gynecomastia**, **increased facial hair growth** or **contralateral testicular atrophy** due to estrogen production.

Patients with Leydig cell tumors might develop **testicular pain** due to **hematoma**. Patients with Sertoli cell tumors might present with **excess estrogen production** and **gynecomastia** as already explained.

Therefore, it has been recommended to perform a **scrotal ultrasound scan** in patients with gynecomastia of unknown cause as it can reveal a testicular mass, and **orchiectomy** has been associated with gynecomastia regression in 80% of the cases.

Diagnostic Work-up for Sex Cord-Stromal Tumors of the Testis

Ultrasonography is the main investigation to be performed in any patient presenting with a testicular mass. It has a very high sensitivity for testicular tumors that can reach 100%. Additionally, patients with gynecomastia of unknown cause might have a **non-palpable intratesticular mass** that can be easily identified with ultrasonography of the scrotum.

Ultrasonography is rarely successful in differentiating between Sertoli cell tumors and germ cell tumors such as seminoma, but can help differentiate giant Sertoli cell tumors of the testis which are associated with **calcification** easily.

Contrast enhanced magnetic resonance imaging of the testes has been found to be more effective in differentiating between sex cord-stromal tumors and germ cell tumors and in the identification of small testicular tumors, but again, **histology** is the only definitive method to confirm the diagnosis of Leydig cell or Sertoli cell tumor.

Abdomino-thoracic computerized tomography scans are indicated once the diagnosis of sex cord-stromal tumor is confirmed because metastasis has been reported in up to 20% of the cases at the time of presentation.

Some **investigative laboratory tests** are being evaluated to increase the certainty of the diagnosis before doing a biopsy. A **low testosterone to estrogen ratio** has been suggested to be evident in patients with sex cord-stromal tumors due to excessive estrogen production by the tumor. **Chorionic gonadotropin administration** has been used to show that estrogenic response in patients with sex cord-stromal tumors is higher than in normal subjects, but this is of limited clinical value.

An important differentiating biomarker between germ cell tumors and sex cord-stromal tumors are the markers **alpha-fetoprotein**, **beta-human chorionic gonadotropin** and **lactate dehydrogenase,** which are always normal in sex cord-stromal tumors.

Treatment of Sex Cord-Stromal Tumors of the Testis

Once the diagnosis of a sex cord-stromal tumor is confirmed, **radical inguinal orchiectomy** is the treatment of choice to achieve the **lowest recurrence rate**. Patients diagnosed with a sex cord-stromal tumor incidentally, i.e. undergone **scrotal ultrasonography** for another indication, might benefit from **testicular sparing surgery** only when **fertility** is an issue and when the tumor is small.

After removing the tumor, the excess estrogenic state is thought to have inhibited the **hypothalamic-pituitary axis** and **hypogonadism** can happen in up to 40% of the cases. On the other hand, patients with endocrinological non-functional tumors, such as germ cell tumors, rarely develop hypogonadism after the radical removal of the affected testis.

Patients with **metastasis** at the time of the diagnosis should not undergo **retroperitoneal lymph node dissection** unless for debulking purposes or staging as it was not found to affect survival. **Combination adjuvant chemotherapy** for patients with recurrent disease includes **bleomycin**, **etoposide** and **cisplatin,** but the response is, unfortunately, short-term and limited.

Radiotherapy is not as effective in sex cord-stromal tumors as it is in seminomas. In fact, one of the reasons for the failure of radiotherapy in a patient with seminoma is misdiagnosis as these patients are later confirmed to have actually had Sertoli cell tumors.
Accordingly, patients with sex cord-stromal tumors should be diagnosed as early as possible to lower the risk of malignancy which is currently estimated to be approximately 20% at the time of the presentation because current adjuvant chemotherapy options, radiotherapy and **retroperitoneal lymph node dissection** add very little to the clinical benefit of the patient.

References

Acar C, Gurocak S, Sozen S. Current Treatment of Testicular Sex Cord-stromal Tumors: Critical Review. Urology 2009; 73: 1165–1171.

Notes