

Educational Case: Testicular Germ Cell Tumor: Clinical Presentation, Pathogenesis, and Diagnostic and Therapeutic Modalities

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289517715040>.¹

Keywords

pathology competencies, organ system pathology, testis, testicular neoplasia, germ cell tumor, tumor markers, risk factors, pathogenesis

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Primary Objective

Objective MT2.1: Germ Cell Tumors of the Testis. Describe the most important risk factors for development of a germ cell tumor of the testis and outline the clinicopathologic features for the different morphologic patterns seen.

Competency 2: Organ System Pathology; Topic: Male Reproductive—Testes (MT); Learning Goal 2: Testicular Neoplasia

Patient Presentation

A 36-year-old male presents to the emergency department with difficulty breathing that began 12 hours ago. The difficulty breathing has worsened progressively over the past 12 hours. He had noticed increasing trouble catching his breath over the last week. In addition, the patient states that he has a large, painless, left testicular lesion, which has been slowly growing for the past 4 months. The patient has a past medical history of left cryptorchidism, status post orchiopexy at age of 4, but otherwise is in good health.

Diagnostic Findings, Part I

The patient was anxious with labored breathing. He had an increased heart rate of 110/minute and an increased respiratory rate of 23/minute. Physical examination revealed multiple rubbery lymph nodes in the left supraclavicular region; the largest one measures 1.5 cm in diameter. Breath sounds were decreased bilaterally on auscultation. Abdomen was soft, non-tender, no rebound, and bowel sounds were normal. A 5 cm, hard and painless mass was palpated in the left testis.

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Questions/Discussion Points, Part 1

What Is Considered in the Differential Diagnosis?

In any man with a solid, firm mass within the testis, testicular tumor must be considered first in the differential diagnosis until proven otherwise. In all young men with a retroperitoneal, supraclavicular, or mediastinal mass, an underlying germ cell tumor should always be considered.² Lymphoma also should be considered in cases with widespread metastatic disease to lymph nodes and other organs, although testicular involvement by lymphoma is uncommon in this young age. The possibility of a widespread metastatic carcinoma, such as urothelial and renal carcinoma, should be evaluated as well. Granulomatous orchitis, testicular abscess, and torsion can also present as a mass; however, they are usually acute onset and accompanied by pain and fever. In addition, they would not have associated lymphadenopathy as this patient has.

What Imaging Should Be Ordered Next?

Scrotal ultrasound is cheap and fast and supplies useful information whether the mass is cystic or solid. Computed tomography (CT) has higher resolution comparing to ultrasound. Given the patient's scrotal mass, lymphadenopathy, and difficulty breathing, it is suspicious for a widely disseminated disease. A full-body CT scan is able to evaluate these areas simultaneously. As a result, it is the choice of imaging examination.

Diagnostic Findings, Part 2

Computed tomography showed multiple bilateral lung nodules, left hydronephrosis, retroperitoneal lymphadenopathy, left supraclavicular lymphadenopathy, and a left testicular heterogeneous mass measuring 5 cm in the greatest dimension.

Questions/Discussion Points, Part 2

Based on the Computed Tomography Findings, What Is the Initial Diagnosis?

Given the multifocality of the lung lesions, they are most likely metastases. The solitary testicular mass seems to be the primary tumor. Because the testis is originated retroperitoneally and descends into the scrotum, testicular tumors are notorious for retroperitoneal lymph node metastasis, as seen in our case.

What Lab Tests Can Be Ordered to Corroborate the Initial Diagnosis?

Testicular carcinoma is the most likely diagnosis based on the imaging findings; therefore, testicular tumor markers should be ordered next. Three serum tumor markers have established roles in the management of men with testicular germ cell tumors: the beta subunit of human chorionic gonadotropin

(β -hCG), alpha fetoprotein (AFP), and lactate dehydrogenase (LDH).

- Beta-hCG is produced by embryonal carcinoma and choriocarcinoma and is the most commonly elevated tumor marker in patients with nonseminomatous Germ Cell Tumor (GCTs). Beta-hCG is also elevated in 15% to 25% of patients with seminomas.³
- Alpha fetoprotein is absent in the serum of normal adults but is detectable in patients with nonseminomatous GCTs and hepatocellular carcinoma. Alpha fetoprotein is not elevated in patients with pure seminomas.
- Lactate dehydrogenase is a less sensitive and less specific tumor marker than β -hCG or AFP for men with nonseminomatous germ cell tumors (NSGCTs) but is elevated in 40% to 60% of men with testicular GCTs.³

Diagnostic Findings, Part 3

The patient had significantly elevated LDH to 2659 U/L (normal <240 U/L), AFP to 18 769 ng/mL (normal <10 ng/mL), and β -HCG to 409 745 mIU/mL (normal <6 mIU/mL). He was transferred to intensive care unit for further management.

Questions/Discussion Points, Part 3

What Is the Significance of the Laboratory Testing, and How Does This Help Establish a Diagnosis/or Differential for This Process?

The level of all 3 markers is markedly elevated, indicating high tumor burden and nonseminomatous components. Lactate dehydrogenase is expressed on chromosome 12p, which is often amplified in testis cancer cells. Lactate dehydrogenase is less specific for testis cancer than HCG or AFP. However, elevated LDH levels are correlated with high tumor burden in seminoma and recurrence in NSGCT.³

What Test Is Needed to Establish the Diagnosis of Testicular Cancer?

Biopsy and histologic examination are helpful to get the definitive diagnosis. Lung biopsy could be done either under the guidance of CT or transbronchially. However, due to the patient's poor condition, he might not be able to tolerate the procedure. Fine needle aspiration (FNA) of the left supraclavicular lymph nodes is feasible because the lymph nodes are superficial, the procedure is less invasive, and the FNA can be accomplished with local anesthesia at bedside.

Trans-scrotal biopsy is considered scrotal violation because the procedure would puncture the scrotal wall, potentially change the lymphatic drainage, and may lead to possible spread to the inguinal nodes.⁴ However, several reports have indicated excellent sensitivity and specificity for FNA biopsy without tumor seeding reported.^{5,6} Diagnosis of lymphoma or granulomatous orchitis through FNA can spare patients radical

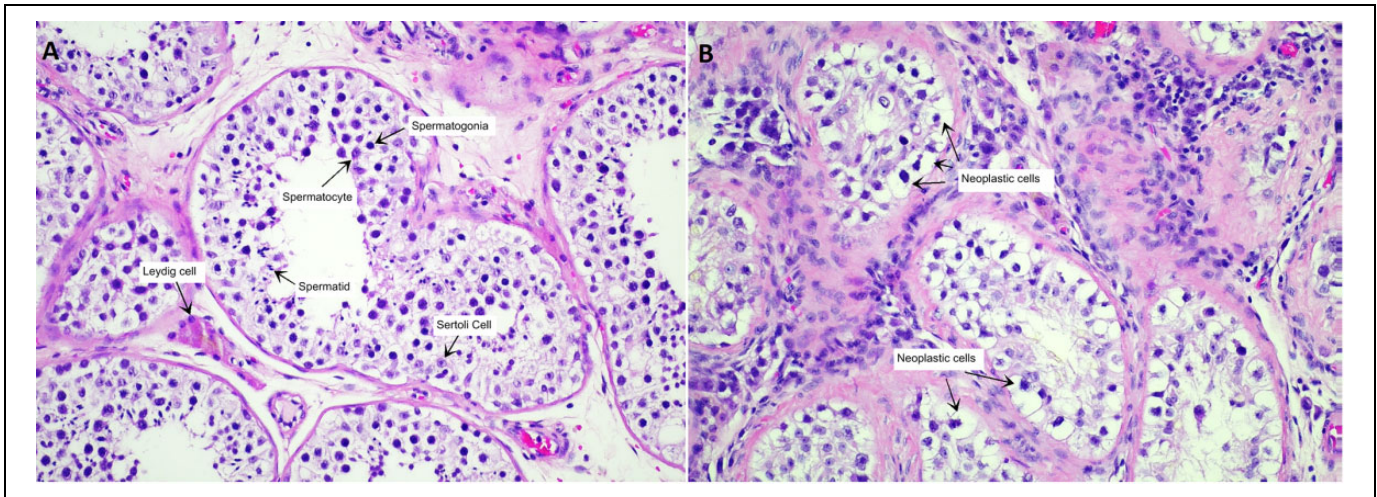


Figure 1. Histologic features. A, Histology of normal seminiferous tubule ($\times 400$). B, Histologic features of germ cell neoplasia in situ (GCNIS). The seminiferous tubules are small and atrophic with no active spermatogenesis. Neoplastic cells are present at the base of the seminiferous tubules. The large neoplastic cells have distinct borders, abundant clear cytoplasm, enlarged round nuclei, and prominent nucleoli ($\times 400$).

orchiectomy. The diagnosis of a testicular malignancy is generally established at radical orchiectomy, which also serves as the initial treatment for the primary tumor. Despite this, there are some men who present with life-threatening advanced disease who undergo systemic chemotherapy prior to orchiectomy (“delayed orchiectomy”). In such patients, the diagnosis should be obtained by biopsy of a metastatic lesion prior to treatment.⁷

Diagnostic Findings, Part 4

The patient underwent left supraclavicular lymph node FNA. The pathology showed nests of seminomatous cells with abundant clear cytoplasm, centrally located nuclei, and distinct cell membranes admixed with primitive, anaplastic cells and yolk sac tumor (YST) component. He was diagnosed with mixed germ cell tumor with components of seminoma, YST, and embryonal carcinoma. The patient received neoadjuvant chemotherapy and stabilized clinically. He further underwent radical left orchiectomy. Surgical pathology revealed residual mature teratoma, fibrosis, and extensive necrosis.

Questions/Discussion Points, Part 4

What Are the Common Risk Factors for Testicular Cancer?

Men with cryptorchidism have an increased risk of testicular cancer. Therefore, prophylactic orchiectomy is generally recommended, especially if the testicle is located in the abdomen.⁸ Inguinal cryptorchidism is less likely to result in malignancy compared with abdominal cryptorchidism; for these men, deferral of surgery with careful surveillance is a reasonable alternative.⁹ Other risk factors include hypospadias, family history, and HIV infection.

What Is the Precursor Lesion to Germ Cell Tumor?

Germ cell neoplasia in situ (GCNIS), previously known as intratubular germ cell neoplasia, is believed to be the precursor to most GCTs.^{10,11} Germ cell neoplasia in situ denotes the development of neoplastic germ cells within the seminiferous tubules. The seminiferous tubules containing GCNIS are usually small or atrophic with a thickened basement membrane. The tubules typically lack active spermatogenesis. The neoplastic cells are enlarged with clear cytoplasm and distinct cell borders. The nuclei are large and hyperchromatic with prominent nucleoli and an irregular nuclear membrane (Figure 1). Germ cell neoplasia in situ has been associated with GCTs of all types in adults discussed below.

What Are the Common Pathologic Types of Testicular Germ Cell Tumors? Briefly Describe Pathologic Features of Each Entity

Seminoma. Seminoma is the most common pure GCT in the testis and accounts for 35% to 50% of all testicular tumors. The mean age of patients is approximately 40 years. Most seminomas are discovered as painless testicular masses. Grossly, seminoma is usually well circumscribed and homogenous. The cut surface appears gray-white. Hemorrhage and necrosis are rarely identified. Seminoma is composed of relatively uniform tumor cells with large round nuclei, prominent nucleoli, discrete cell borders, and usually clear cytoplasm. Tumor cells grow in sheets or nests separated into lobules by fibrous septa containing small lymphocytes (Figure 2).

Embryonal carcinoma. Embryonal carcinoma is the second most common pure testicular germ cell neoplasm after seminoma. In contrast to seminoma, the tumor is usually poorly circumscribed with a variegated, soft cut surface. Necrosis and hemorrhage are common. Embryonal carcinoma comprises of

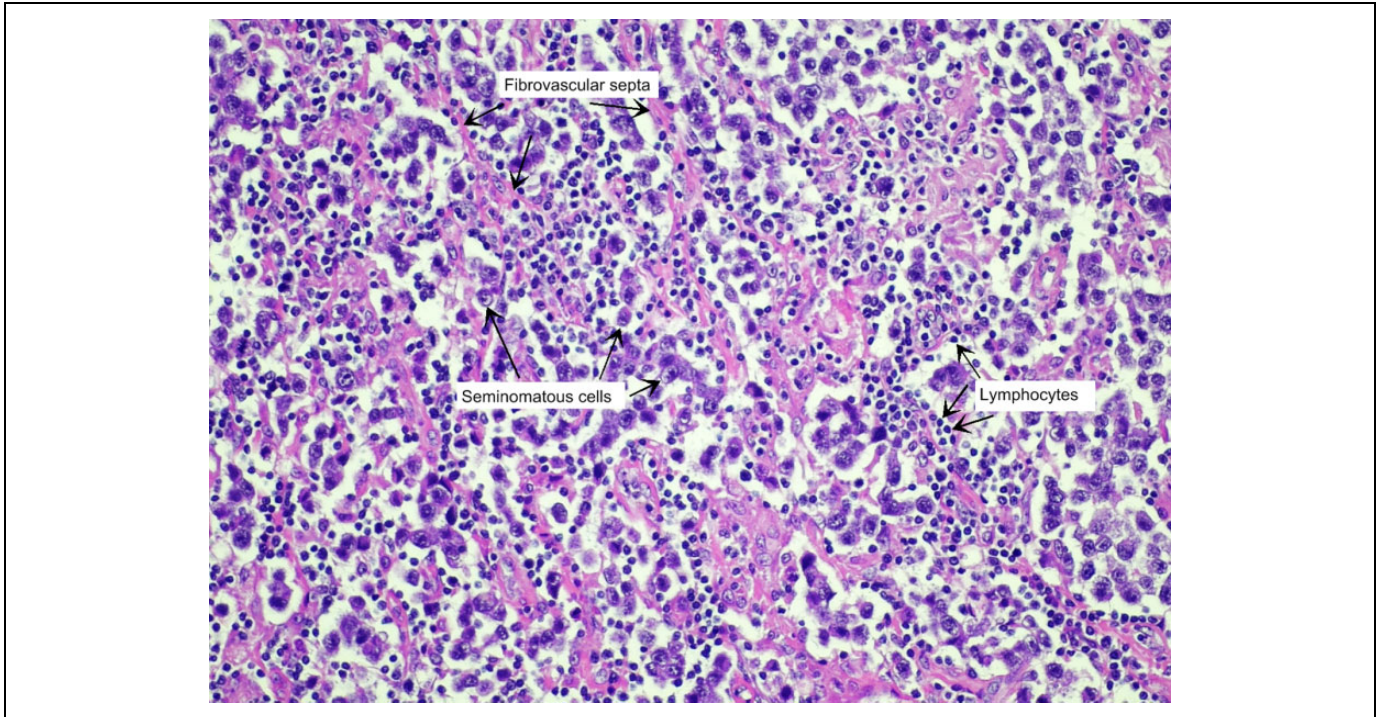


Figure 2. Histologic features of seminoma. This photomicrograph shows nests of uniform seminomatous cells with abundant clear cytoplasm, centrally located nuclei, and distinct cells membranes. Fibrovascular septa with small lymphocytes are characteristic of seminoma ($\times 200$).

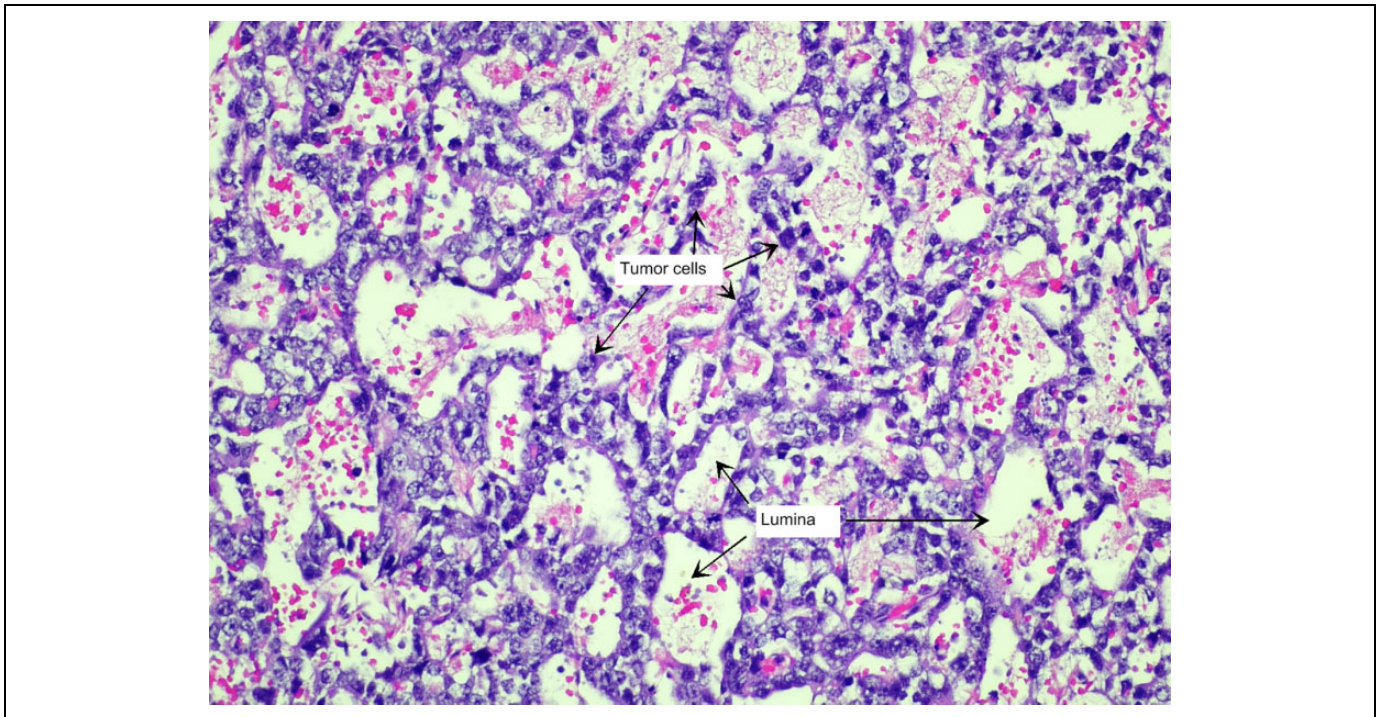


Figure 3. Histologic features of embryonal carcinoma. Embryonal carcinomas are composed of primitive, anaplastic cells. The image shows tubular/glandular pattern in which cuboidal to columnar cells form gland-like or tubule-like structures. The enclosed lumina are cleft-like or round ($\times 400$).

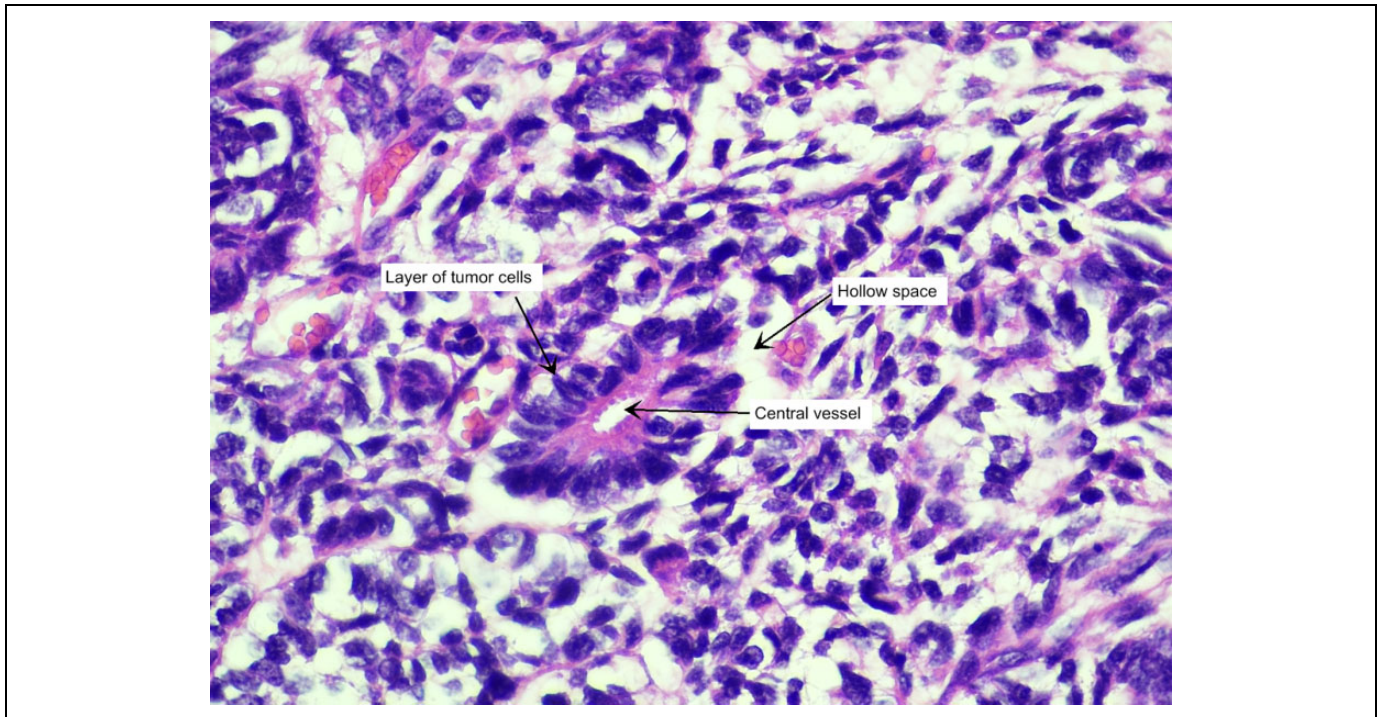


Figure 4. Histologic features of yolk sac tumor (YST). This image shows a Schiller-Duval body in YST, which is characterized by a central vessel surrounded by a layer of tumor cells, a hollow space, and another layer of similar or more flattened cells, again set in an empty space ($\times 400$).

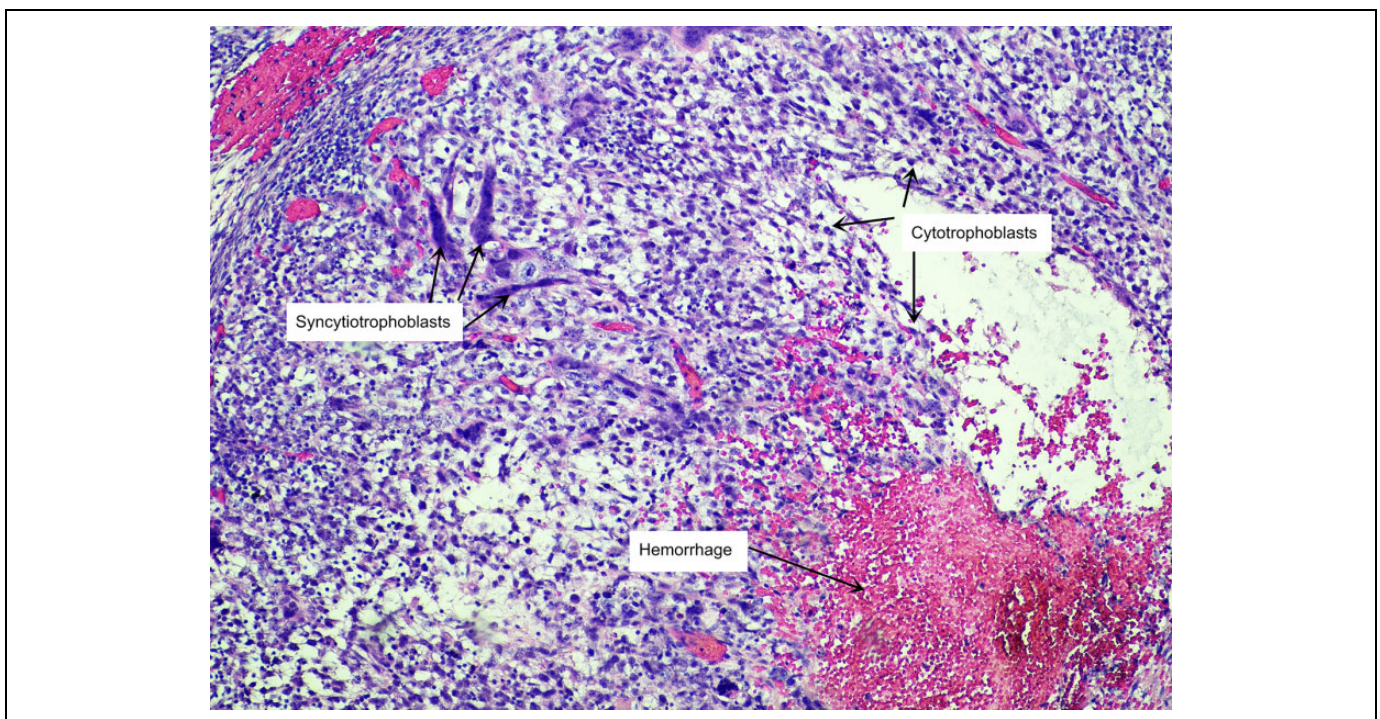


Figure 5. Histologic features of choriocarcinoma. Intimate admixture of mononucleate cytotrophoblasts with clear cytoplasm and a few multinucleate syncytiotrophoblasts are characteristic of choriocarcinoma. Hemorrhage is present ($\times 200$).

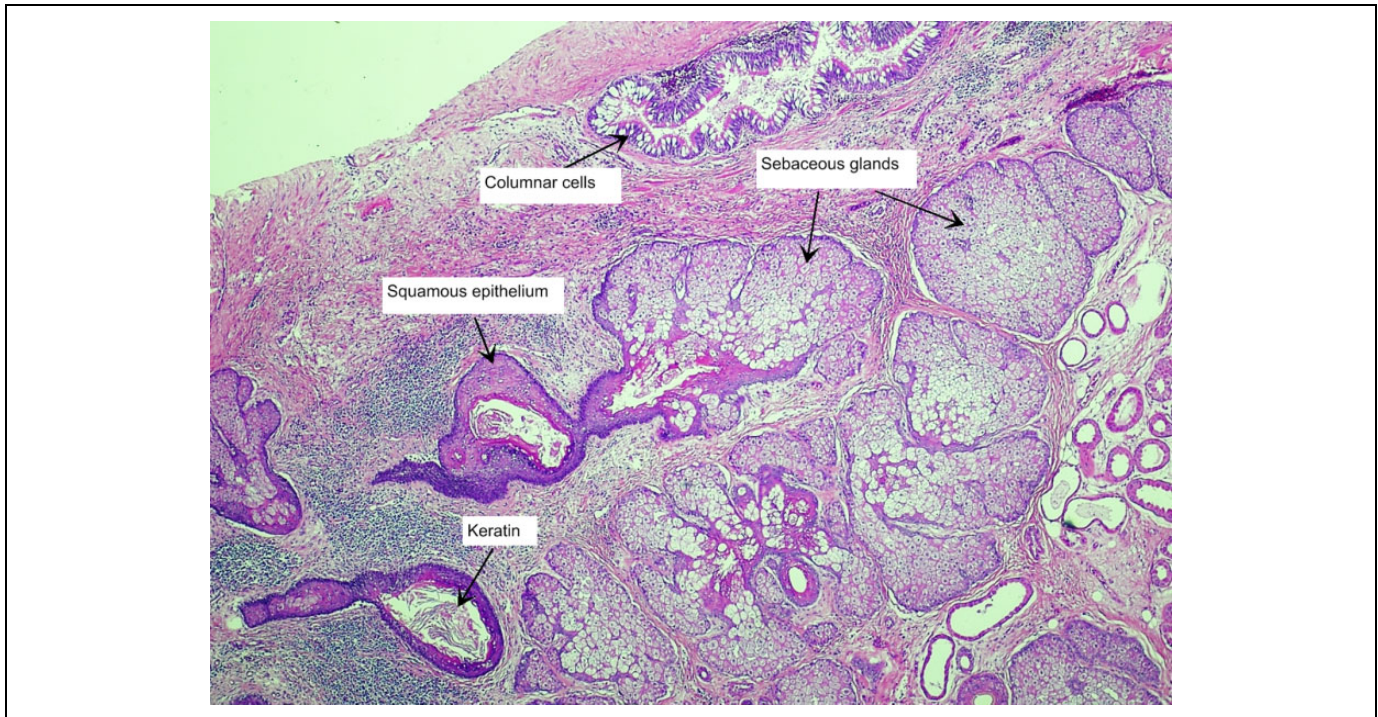


Figure 6. Histologic features of teratoma. Teratoma consists of squamous epithelium, sebaceous gland, and ciliated columnar cells. Keratin can also be noted ($\times 200$).

primitive epithelial tumor cells in a variable growth pattern that recapitulates an early phase of embryogenesis. Embryonal carcinoma commonly shows 3 growth patterns: solid, glandular, and tubulopapillary (Figure 3).

Yolk sac tumor. Yolk sac tumor, also known as endodermal sinus tumor, displays a variety of morphologic patterns that resemble the embryonic yolk sac, allantois, and extraembryonic mesenchyme.¹² Yolk sac tumors show a wide variety of growth patterns, which often merge from one to another. The most common pattern is the microcystic or reticular pattern, composed of numerous small, thin-walled cysts lined with flattened cells with scant cytoplasm that produce a reticular appearance. Yolk sac tumor is characterized by Schiller-Duval bodies, which are composed of a thin-walled blood vessel surrounded by an edematous space and a layer of cuboidal to columnar cells with prominent nuclei and clear cytoplasm (Figure 4). The presence of YSTs in mixed GCTs, particularly in metastasis, may worsen the patient's prognosis.¹²

Choriocarcinoma. Choriocarcinoma is a germ cell tumor composed of syncytiotrophoblasts, cytotrophoblasts, and intermediate trophoblasts, which produce a large amount of β -hCG (Figure 5). The tumors often show a hemorrhagic nodule with a solid tan to gray rim in the periphery. The hemorrhage is usually extensive with blood clots, and necrosis is common.

Teratoma. Testicular teratoma contains more than one germ cell layer in various stages of maturation and differentiation.

Morphologically, it is identical to teratoma in other parts of the body (Figure 6). Testicular teratomas may present in both prepubertal and adult males, but the prognosis differs greatly between these 2 age groups. In children, teratomas most often occur before the age of 4, are generally seen in their pure form, and behave in a benign fashion.¹³ In adults, despite their benign histologic appearance, teratomas are frequently found at metastatic sites and contain many genetic abnormalities frequently found in malignant germ cell tumor elements.¹⁴ Therefore, it's regarded as malignant component. Teratoma is resistant to chemotherapy.

Mixed germ cell tumors. Mixed germ cell tumor is composed of at least 2 different germ cell tumor histologic types and comprises approximately one-third of all testicular GCTs.¹⁵ The tumor shows a variegated appearance, and the appearance reflects the tumor composition. There may be cystic, solid, soft, firm, hemorrhagic, and necrotic areas. Any combination of germ cell tumor types may be present in the testis. The most common combinations are embryonal carcinoma and teratoma, followed by embryonal carcinoma and seminoma. Each type in mixed germ cell tumor shows histologic features similar to those corresponding to the pure form.

What Is the Metastatic Route for Testicular Germ Cell Tumors?

With the exception of choriocarcinoma, which demonstrates early hematogenous spread, germ cell tumors of the testis

typically spread in a stepwise lymphatic fashion. Lymph nodes of the testis are concentrated at the level of the renal hilum because of their common embryologic origin with the kidney. The retroperitoneum is the initial site of metastatic spread in 70% to 80% of patients with GCT.¹⁶

The primary landing site for the right testis is the interaorto-caval area at the level of the right renal hilum. Stepwise spread, in order, is to the precaval, preaortic, paracaval, right common iliac, and right external iliac lymph nodes. The primary landing site for the left testis is the para-aortic area at the level of the left renal hilum. Stepwise spread, in order, is to the preaortic, left common iliac, and left external iliac lymph nodes.¹⁷

Describe the Classification System of Testicular Cancer? What Is Unique to the Staging of Testicular Cancer?

Testicular cancer is staged using the tumor, node, metastasis (TNM) staging system developed jointly by the American Joint Committee on Cancer and the Union for International Cancer Control, which applies to both seminomas and NSGCTs.¹⁸

Of note, size of 3 cm, lymphovascular, tunica albuginea, epididymal, tunica vaginalis, and scrotum invasion are the key points in T staging. Due to the embryonic development of testis, retroperitoneal lymph node metastasis is regarded as regional lymph node metastasis instead of distant metastasis. Sizes of 2 and 5 cm are the cut points in N staging.

Unique to testicular cancer is the addition of S, which refers to serum tumor markers to the staging system. The extent of elevation of these tumor markers is an important prognostic marker for patients with GCTs. It is important to note that for the purposes of TNM staging, the serum tumor markers should be assessed only after orchiectomy has been completed.

What Is the Most Common Genomic Change Seen in Germ Cell Tumors?

The characteristic genomic change in the pathogenesis of GCTs is located on chromosome 12p. An isochromosome of 12p, or i(12p), is found in 80% of patients with GCTs, regardless of the GCT histologic type. An isochromosome is an unbalanced structural abnormality in which the arms of the chromosome are mirror images of each other.¹⁹ Several candidate genes have been associated with the gain of 12p, including KRAS2, cyclin D2, and DAD-R.¹²

How Is Testicular Germ Cell Tumor Categorized From the Standpoint of Treatment? What Is the Rationale of the Categorization?

Testicular germ cell tumors are categorized into 2 broad categories: seminoma and NSGCT. Nonseminomatous germ cell tumor includes embryonal carcinoma, teratoma, choriocarcinoma, and YST. Any of the above present in a testicular tumor makes it an NSGCT, even though there might be a component of seminoma. The main reason to group testicular tumor is for

the ease of selecting treatment modality. Seminoma responds well to both radiation and chemotherapy. However, NSGCT is sensitive to chemotherapy only and do not respond well to radiation. Therefore, mixed germ cell tumor, even though with a large proportion of seminoma, is treated as a NSGCT, which doesn't not respond well to radiation.

Teaching Points

- Cryptorchidism is the most common risk factor for testicular tumor.
- Seminoma is the most common pure germ cell tumor in the testis. It is characterized by uniform tumor cells with large round nuclei, prominent nucleoli, clear cytoplasm, and dense lymphocytes in the fibrous septa. It is exquisitely sensitive to radiation therapy.
- Teratoma identified in a mixed germ cell tumor has deceptively benign morphology. However, it's a malignant component.
- Testicular biopsy is contraindicated in patients with a testicular mass.
- Retroperitoneal lymph node is the most common site of regional lymph node metastasis due to embryonic origin of the testis.
- Serum tumor markers (LDH, AFP, and β -hCG) are incorporated into the TNM staging system for testicular cancer. Elevated LDH level is correlated with high tumor burden. Elevated levels of AFP or β -hCG are indicative of NSGCT.
- Mixed germ cell tumor containing seminoma is categorized as NSGCT from the treatment perspective. It's treated with chemotherapy regimen for NSGCT. Don't be misled by the name.

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