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Educational Case

Educational Case: Classic seminoma of the testis

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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 https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme.[1]

Keywords: Pathology competencies, Organ system pathology, Male reproductive, Testicular neoplasia, Germ-cell tumors of the testis, Diagnosis of the testicular mass, Seminoma

Primary objectives

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 MT: Male Reproductive—Testes; Learning Goal 2: Testicular Neoplasia.

Objective MT2.2: Diagnosis of the Testicular Mass. Discuss a differential diagnosis for a testicular mass.

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

Patient presentation

A 50-year-old man with a past medical history of hydrocele presents for scrotal swelling. The swelling is bilateral, painless, and has gradually increased in size since it was first noticed 3 months ago. He denies dysuria, hematuria, frequency, fevers, chills, weight changes, abdominal or back pain, or recent injury to the area. Other medical history includes hypertension. There is no history of cryptorchidism, no prior surgeries, and no family history of cancer. He endorses occasional alcohol use but no tobacco use.

Diagnostic findings, Part 1

Physical examination reveals a well-appearing male with vitals within normal limits. In addition to bilateral hydroceles, the testicular exam reveals a firm and enlarged left testis measuring 6 cm with a palpable, smooth, nontender mass and mobile overlying skin. The testes are nonerythematous and do not change in size with cough. The enlarged testis shows limited transillumination. The patient does not have any inguinal, axillary, or cervical lymphadenopathy. The remainder of the patient's exam is unremarkable.

Questions/discussion points, Part 1

What is the differential diagnosis of a painless testicular mass? What physical examination technique may be helpful to narrow the differential?

The differential diagnosis for this patient's presentation of a persistent painless testicular mass includes testicular neoplasms such as germ cell tumor (GCT), sex cord stromal tumor, or lymphoma, as well as lesions of the scrotal sac such as hydrocele, varicocele, epididymal cyst, and hernia.[2] Testicular masses may be solid, as seen in most testicular neoplasms, or cystic, as seen with hydroceles.[3] The physical exam technique of transillumination, in which the examiner shines a light through the mass, can help to differentiate between solid and cystic lesions, as light will pass through a cystic lesion but not a solid one. However, it is important to note that solid lesions can still occasionally be associated with reactive hydrocele formation.[4] Although neoplasms may be painful in 20% of cases,[2] most painful testicular lesions, such as torsion, incarcerated hernia, and abscess, typically have infectious or traumatic etiologies.[4] Because of this variability in presentation, palpable testicular nodules or masses should be assumed neoplastic until proven otherwise.[4]

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What diagnostic studies should be ordered?

Scrotal ultrasound is first-line diagnostic imaging for evaluation of a testicular mass and should be ordered immediately if there is any suspicion for a neoplasm given the potential for rapid growth and disease progression.[4,5] The scrotal ultrasound is crucial in confirming the presence of a mass, its location relative to the testis, and involvement of the contralateral testis.[5] Ultrasound may also exclude other benign causes of painless testicular lesions such as varicoceles.[2] Other imaging studies, such as chest X-ray and abdominal/pelvic CT with contrast to evaluate for pulmonary or retroperitoneal involvement, may also be considered. Routine laboratory studies, including serum electrolytes, complete blood count (CBC), and liver function tests (LFTs), are useful in demonstrating hematological abnormalities that could suggest lymphoma, infectious/inflammatory process related to an abscess or infarcted tissue, or possible liver involvement.[5] If concern for neoplasm remains after routine labs and imaging, chest CT and PET or nuclear medicine scan can be ordered to evaluate for metastasis.[5]

Diagnostic findings, Part 2

Scrotal ultrasound demonstrates an enlarged left testis with a homogeneous and hypoechoic mass, concerning for malignancy (Fig. 1). A moderate bilateral hydrocele is also observed. Based on the ultrasound findings, additional radiographic and laboratory studies are performed. Abdominal/pelvic CT reveal sclerotic foci on the patient's iliac crests but did not show any retroperitoneal lymph node enlargement. Chest CT shows multiple pulmonary nodules and scleral foci in 2 ribs. Routine laboratory studies demonstrate electrolytes, LFTs, and CBC within normal limits.

Questions/discussion points, Part 2

How can the scrotal ultrasound findings be interpreted to narrow the differential diagnosis?

A solid mass in the testis frequently indicates malignancy, and particular ultrasound features may be associated with certain types of neoplasms.[6] Seminomas typically demonstrate well-defined, circumscribed or lobulated borders and homogenous appearance, as seen in this case.[6] Masses with ill-defined borders, heterogeneous appearance, or cystic components are more likely to represent nonseminomatous or mixed GCTs or less frequently lymphoma or spermatocytic tumor.[6]

What is the role of biomarkers in evaluating testicular cancer?

When evaluating a testicular mass, evaluating serum tumor biomarker levels before any surgical or other therapeutic intervention is crucial. Tracking serum tumor biomarker levels before and after surgical or antineoplastic therapy assists in monitoring disease stability or progression, evaluating treatment efficacy, predicting prognosis, and detecting remission or recurrence through both biomarker levels and rate of change in certain biomarkers.[5,7] The classic biomarker panel for testicular tumors includes alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (βhCG), and lactate dehydrogenase (LDH). AFP and hormone subunit βhCG levels are more specific to tumor and tumor types (i.e., Elevated AFP for yolk sac tumor and βhCG for choriocarcinoma), while LDH is less specific and better informs overall tumor burden.[7] While particular testicular tumors exhibit characteristic biomarker profiles (Table 1[4,7–11]), these biomarkers have low sensitivity and specificity for predicting final diagnosis.[7]

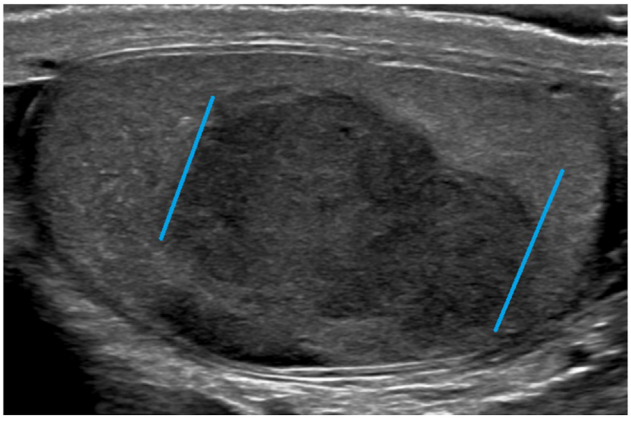

Fig. 1. Scrotal ultrasound. Scrotal ultrasound demonstrates enlarged left testis with a homogenous, hypoechoic mass (between blue lines).

Diagnostic findings, Part 3

The patient's tumor biomarker panel reveals an AFP level of 3.0 ng/mL (ref range: <6.1 ng/mL), βhCG of <2.0 mIU/mL (ref range: <5 mIU/mL), and LDH of 300 U/L (ref range: 110–240 U/L).

Questions/discussion points, Part 3

How can this patient's tumor biomarker panel be interpreted?

Out of the 3 biomarkers, only LDH is elevated compared to the reference range. Elevated LDH suggests some degree of tumor burden for this patient but does not implicate a specific type of neoplasm. The absence of serum AFP and βhCG abnormalities makes it difficult to narrow down to a single differential diagnosis but helps to exclude yolk sac

Table 1
Features of germ cell tumors.[4,7–11]

Germ Cell Tumor (GCT) Subtype	Frequency of Subtype	Most Affected Age	Elevated Serum Tumor Biomarkers[a]	Common IHC Markers[a]
Seminoma	35–70%	30–40 yo	βhCG[b], LDH	PLAP, c-kit, OCT4, hCG[b], SALL4, SOX17[b]
Embryonal Carcinoma	3–4%	20–40 yo	LDH	PLAP, OCT4, CD30, cytokeratin, SALL4, SOX2
Yolk Sac Tumor	65% *(prepubertal)* 2.4% *(postpubertal)*	<10 yo	AFP, LDH	PLAP, AFP, cytokeratin, A1AT, albumin, ferritin, SALL4, GPC3
Teratoma	35% *(prepubertal)* 2.7–7% *(postpubertal)*	<4 yo	LDH, variable	AFP, tissue-specific markers, SALL4
Choriocarcinoma	<1%	20–40 yo	βhCG, LDH	hCG, hPL, placental glycoproteins, PLAP, cytokeratins, SALL4, GPC3
Spermatocytic Tumor	1.2–4.5%	>40 yo	LDH	Cytokeratins, SALL4
Mixed GCT	60%	20–40 yo	[c]	[c]

[a] Biomarker and Immunohistochemistry (IHC) abbreviations: βhCG = beta human chorionic gonadotropin. LDH = lactate dehydrogenase. AFP = alpha-fetoprotein. PLAP = placental alkaline phosphatase. OCT4 = octamer-binding transcription factor 4. SALL4 = Spalt Like Transcription Factor 4. A1AT = alpha-1 antitrypsin. GPC3 = glypican 3. hPL = human placental lactogen.
[b] If syncytiotrophoblasts are present.
[c] Laboratory characteristics are dependent on the composition of mixed germ cell tumors. Most common combinations include embryonal, yolk sac, and teratoma components.[5]

tumor and choriocarcinoma elements in which elevation in these biomarkers would be expected (see Table 1).[5,7] Overall, these findings are nonspecific, and gross and histological examination of the excised testis will be needed for final classification.

What is the initial management of testicular tumors?

Radical inguinal orchiectomy of the affected testis is the indicated management for the majority of testicular tumors.[4,5] This procedure, involving the removal of the testis and spermatic cord to the internal inguinal ring, is both a therapeutic and diagnostic intervention for most testicular neoplasms.[4,5] Testicular tumors are not typically biopsied prior to surgery due to the risk of seeding malignant cells into the surrounding scrotum and disrupting lymphatic drainage patterns.[4,8]

Diagnostic findings, Part 4

A radical orchiectomy is performed. The gross and histologic findings are seen in Figs. 2 and 3.

Questions/discussion points, Part 4

What are the notable gross features in this case, as seen in Fig. 2, and of which common testicular tumor are they most characteristic?

This lesion is grossly characterized as well-circumscribed, tan-white, and homogeneous in appearance. Features absent in this case include hemorrhage, necrosis, or mucoid cysts over the cut surface, making several types of testicular neoplasm less likely, such as embryonal carcinoma, choriocarcinoma, yolk sac tumor, and spermatocytic tumor.[9] Overall, the gross appearance of the lesion, which measures 6.1 cm × 5.1 cm × 3.2 cm, extends to the tunica albuginea, and does not involve the spermatic cord, is most characteristic of a seminoma which typically presents as a large, bulky lesion with a nodular appearance.[9]

What are the notable histologic features in this case, both within the mass as seen in Fig. 3A and B and in the adjacent testicular tissue as seen in Fig. 3C and D? Of which common testicular tumor are these features most characteristic?

This case features sheets of monomorphic cells with large central nuclei, 1–2 prominent nucleoli, clear cytoplasm, and well-defined cell borders separated by fibrovascular septae with lymphocytic infiltrate. No glandular structures are seen, and GCNIS is present in the adjacent seminiferous tubules. Overall, these findings are most characteristic of seminoma. Full microscopic examination also reveals focal involvement of the tunica albuginea. No lymphovascular invasion is identified.

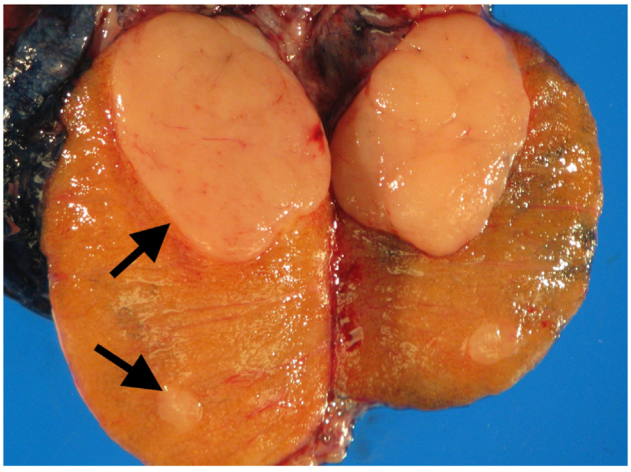

Fig. 2. Gross appearance of seminoma. A cross section of an example excised testis demonstrates 2 foci of bulky, tan-white seminoma (arrows) without associated hemorrhage or necrosis.

Characteristically, seminomas are comprised of large round or polygonal cells with distinct cell membranes, clear cytoplasm, a large central nucleus, and 1–2 prominent nucleoli. Malignant cells are usually organized in nests, sheets, or lobules divided by lymphocyte-containing fibrous septae.[9,10] Small granulomas may also be seen.[10] GCNIS, a noninvasive precursor lesion to seminomas, are often seen in neighboring testicular tissue.[9,10] GCNIS is differentiated from normal spermatogenesis in testicular tissue on histology (Fig. 3C and D) by identifying groups of large cells resembling those of seminoma confined within the tubules.[9] GCNIS may be seen in association with other germ cell tumors (GCTs), as well. It should be noted that in up to 25% of cases, seminomas may also contain syncytiotrophoblasts, which appear as multinucleated giant cells with vacuolated cytoplasm, which do not represent a component of choriocarcinoma.[4,7,9] Although seminomas do not display distinct glandular structures, they may occasionally appear tubular or microcytic, leading to diagnostic confusion with yolk sac tumors.[10]

In what category of lesions do seminomas belong?

Seminomas fall into the category of germ cell tumors, which are the most common solid tumors in young adult males and make up 95% of testicular tumors overall.[4,5]

What are the pathologic features of GCTs as a broader category? What lesions do they include? How are these lesions differentiated from seminoma?

According to the World Health Organization, in addition to seminoma, GCTs also include yolk sac tumor, embryonal carcinoma, choriocarcinoma, teratoma, and spermatocytic tumor, with all but prepubertal teratoma, yolk sac tumor, and spermatocytic tumor typically associated with GCNIS on histology.[12] While more than half of GCTs have a mixed composition containing more than one histologic pattern,[5] seminomas are the most common of the pure GCTs.[9]

Although some overlap exists, the various types of GCT can be differentiated in most cases through evaluation of the gross and microscopic features. The typical histology of nonseminomatous GCTs is depicted in Fig. 4. In the current case, the uniformity of the lesional cells is not seen in embryonal carcinomas, which generally display much more anaplasia and areas of necrosis (Fig. 4A).[9,10] This uniformity and absence of organoid structures is also uncharacteristic of yolk sac tumors, which have a variable but distinct morphologic patterns resembling various extraembryonic structures and endodermal tissues (Fig. 4B), and teratomas, which recapitulate many somatic tissue types (Fig. 4C).[9] If choriocarcinoma were present, mixed trophoblastic cell types, multinucleated syncytiotrophoblasts, and areas of hemorrhage would likely be seen, also features absent from this case (Fig. 4D).[9] The pathologic features of GCT types are discussed in greater detail in a previously published educational case by Wang L et. al.[13]

What are the risk factors for GCTs?

Known risk factors for GCTs include prior cryptorchidism, previous testicular cancer in either testis, prior infertility, and untreated human immunodeficiency virus infection.[4,5,8] Genetics are also a known factor as family history of GCT in a first-degree male relative, as well as Down's Syndrome, are associated with increased risk.[4,14] In fact, 6 loci on 4 chromosomes have been associated with GCT development.[14] Regarding environmental and occupational factors, some studies suggest that frequent exposure to pesticides, polyvinyl chloride plastic, heavy metals, and nonionizing radiation may be risk factors for GCT, although further investigation is needed.[14]

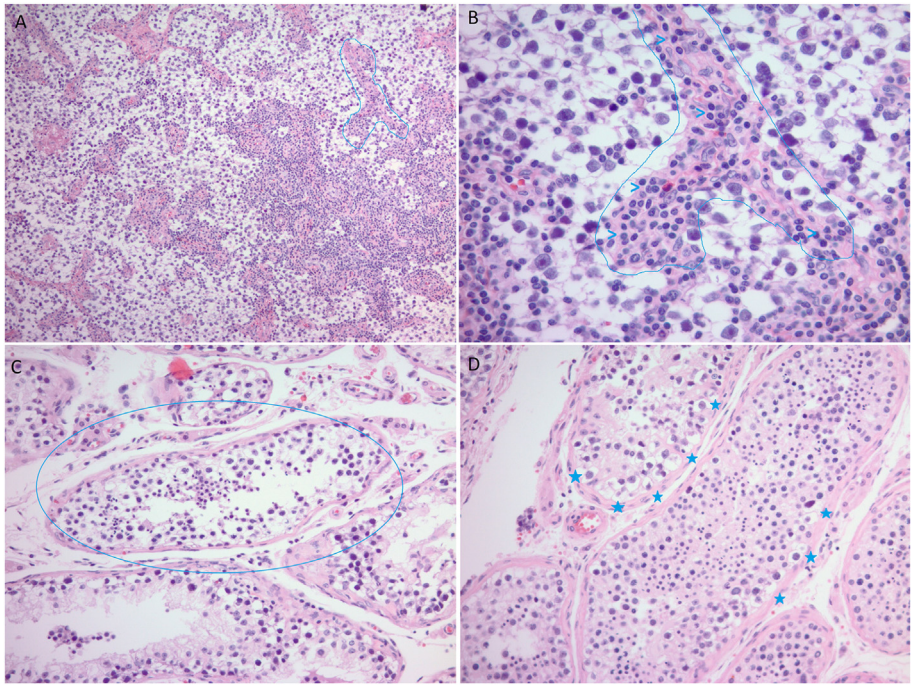

Fig. 3. Histologic appearance of testicular mass. A hematoxylin and eosin-stained tissue section demonstrates sheets of monotonous cells with clear cytoplasm and fibrous septae (outlined in blue) with associated lymphocytic infiltrates (angle brackets), consistent with seminoma (A [10 × objective], B [40 × objective]). Additional hematoxylin and eosin-stained tissue sections demonstrate adjacent (C [20 × objective]) normal seminiferous tubules with intact spermatogenesis (blue circle) and (D [20 × objective]) seminiferous tubules involved by GCNIS with malignant germs cells (stars) undermining and replacing the normal cellular architecture.

What other technique can be performed to help differentiate seminoma from other GCTs, and how?

Seminomas can be further characterized and differentiated from other GCTs by immunohistochemistry. Seminomas typically express placental alkaline phosphatase (PLAP), octamer-binding transcription factor 4 (OCT4), c-kit (CD117), and Spalt-like transcription factor 4 (SALL4), as well as hCG in syncytiotrophoblasts, if present.[9–11] Diffuse PLAP staining is characteristic of seminomas but can also be increased in tissue from patients that smoke.[7] In contrast to embryonal

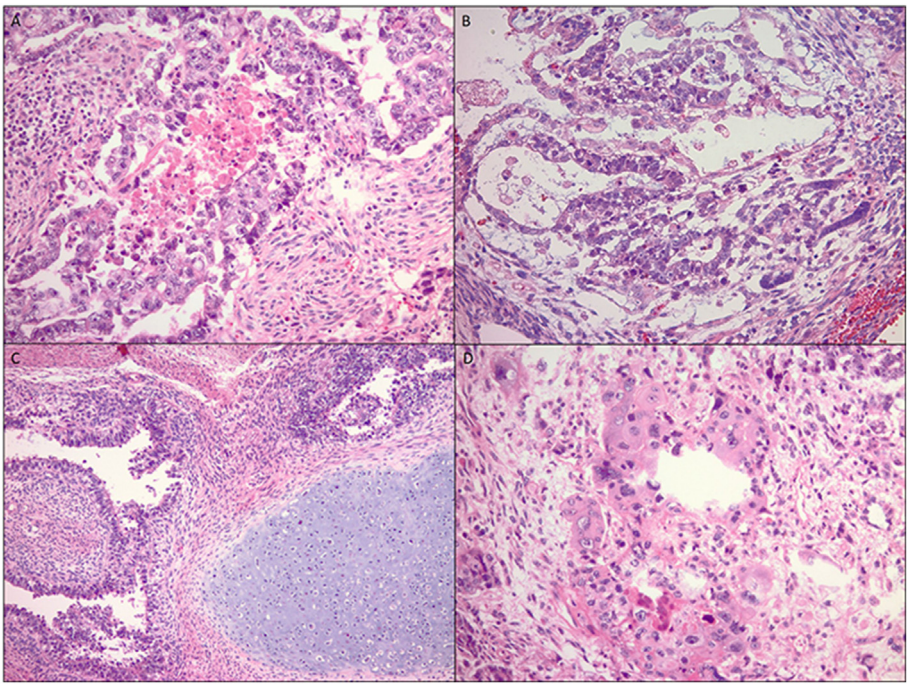

Fig. 4. Histologic appearance of nonseminomatous GCTs on hematoxylin and eosin-stained tissue sections. Embryonal carcinoma (A [20 × objective]) demonstrates significant anaplasia and areas of necrosis (central pink amorphous material). Yolk sac tumor (B [20 × objective]) exhibits variable, sometimes organoid, morphologic patterns composed of cuboidal cells with clear cytoplasm. Teratoma (C [10 × objective]) recapitulates mature and immature somatic tissue types, such as cartilage and respiratory epithelium, as seen in this case, among others. Choriocarcinoma (D [20 × objective]) is composed of aggregates of mixed trophoblastic cells and multinucleated syncytiotrophoblasts with associated hemorrhage (not seen in this case).

carcinomas, seminomas show absent or only focal staining for CD30, SOX2, and cytokeratins.[10,11] Glypican 3 staining, seen in yolk sac tumors and most choriocarcinomas, is absent in seminomas.[11] Although typically distinguishable based on histology, seminomas featuring syncytiotrophoblasts may be separated from choriocarcinomas by positive staining for SOX17.[11] Immunohistochemistry of GCTs is further discussed in Table 1.

What are the clinical and laboratory characteristics of seminoma?

Patients with a seminoma usually present with a large, painless or sometimes painful, unilateral intratesticular mass, typically larger than 5 cm.[5] Only 1–5% of all GCT cases are estimated to be bilateral.[15] The most common bilateral testicular neoplasm is diffuse large B-cell lymphoma, the most common primary lymphoma of the testes.[4] Patients with seminoma may experience gynecomastia, a paraneoplastic symptom resulting from the presence of βhCG-secreting syncytiotrophoblasts in some cases.[5] It should be noted that this phenomenon is not specific to seminomas and may arise in nonseminomatous GCTs that secrete βhCG.[16] As most GCTs, including seminomas, demonstrate lymphatic spread, common sites of metastasis include the retroperitoneal to supraclavicular lymph nodes and lungs.[9] For this reason, symptoms of back or flank pain, shortness of breath, hemoptysis, or neck mass are suggestive of nodal and/or pulmonary metastases.[4]

The serum tumor biomarker panel for seminomas typically demonstrate elevated LDH and occasionally elevated βhCG if syncytiotrophoblasts are present, with normal AFP.[4,7] AFP elevation should raise suspicion for nonseminoma GCT such as yolk sac tumor, a mixed GCT, or alternate diagnoses (see Table 1).[7]

What underlying molecular aberrations are seen in GCTs?

The primary molecular aberration identified in GCNIS and all subtypes of GCT is duplication of the short arm or "p" arm of chromosome 12, forming an isochromosome (fusion of the 2 p arms) known as i(12p).[17] In addition, activating mutations of the KIT tyrosine kinase receptor (KIT) are identified in approximately 25% of seminomas and have been identified in GCNIS, as well.[17] Aberrations in signaling through the KIT and BAK pathways have also been implicated in familial germ cell tumor predisposition syndromes.[17]

Diagnostic findings, Part 5

Serum tumor biomarker levels taken 2 months postorchiectomy demonstrate an LDH of 167 U/L, βhCG of <2 mIU/mL, and AFP of 1.8 ng/mL. A comparison to preorchiectomy levels can be seen in Table 2. Serum electrolytes and CBC continue to be within normal limits.

This patient undergoes a PET scan revealing no definitive evidence of pulmonary or bone metastases. Multiple biopsies of the sclerotic bone lesions demonstrate no evidence of metastases to bone. The patient's status is monitored with active surveillance with follow-up approximately every 2 months. Subsequent exams are unremarkable, with repeat chest and pelvic imaging showing no concerning changes, and biomarkers remain stable and within normal limits over the next 5 years.

Questions/discussion points, Part 5

How are germ cell tumors staged?

All GCTs are staged using the TNM + S staging system (Tumor, Lymph Node, Metastases, Postorchiectomy Serum Tumor Biomarkers).[4,5,7] According to the American Joint Committee on Cancer (AJCC) guidelines, stage I testicular cancers are those limited to the testis without nodal or metastatic involvement, stage II those with retroperitoneal lymph node involvement or persistent biomarker elevation, and stage III those with distant metastases.[4,5] Over 80% of patients initially present at stage I.[5] Risk stratification of stage IIC and III GCTs are also based on TNMS classification.[4]

Table 2
Preorchiectomy and 2-month postorchiectomy tumor biomarker levels.

	AFP (ng/mL)[a]	βhCG (mIU/mL)[a]	LDH (U/L)[a]
Reference Range	<6.1	<5.0	110–240
Preorchiectomy	3.0	<2.0	300
Postorchiectomy	1.8	<2.0	167

[a] Biomarker abbreviations: AFP = alpha-fetoprotein. βhCG = beta human chorionic gonadotropin. LDH = lactate dehydrogenase.

What is this patient's stage?

Based on this patient's pathologic findings demonstrating seminoma confined to the testis, normalized postorchiectomy serum tumor biomarkers, and absence of nodal or distant metastases, this case is stage I.

What is the prognosis of seminoma, and what treatments are available?

Seminomas generally have an excellent prognosis.[4] These tumors are typically less aggressive than nonseminoma GCTs and respond well to radiotherapy and chemotherapy.[8] Even at advanced stages, seminomas pose good (95% cure rate) to intermediate risk (80–90% cure rate).[4] This prognosis may also be attributed to the overall good health of the young adult patients most frequently affected by the disease.[7]

Postorchiectomy treatment may include active surveillance, radiotherapy, or platinum-based chemotherapy. With a 99% 5-year survival rate and a 15–17% 5-year risk for relapse, stage I seminomas are often treated with active surveillance alone, which involves frequent physical exams, serum biomarker level readings, and abdominal and chest imaging for 5 years.[4,5] Adjuvant radiotherapy and/or chemotherapy, with retroperitoneal lymph node dissection as needed, is routine for higher stage seminomas, with a 98–99% 5-year survival rate for stage II and over 80% 5-year survival for stage III.[4,5] Note that mixed tumors with a seminoma component are treated like nonseminoma GCTs, which follow a different treatment algorithm and risk stratification.[4,5] Additionally, due to the effect of radiotherapy and chemotherapy on spermatogenesis, patients may consider pursuing sperm banking or cryopreservation before initiating adjuvant therapy.[4]

Teaching points

- The differential diagnoses for testicular mass include neoplastic processes such as GCT or lymphoma, as well as non-neoplastic processes such as hydroceles.
- GCT types include seminoma, embryonal carcinoma, yolk sac tumor, teratoma, choriocarcinoma, and the rare spermatocytic tumor.
- Major risk factors for GCTs include cryptorchidism, history of infertility or testicular cancer, and family history of testicular cancer.
- Serum tumor biomarkers, including AFP, βhCG, and LDH, are essential staging and prognostic indicators for GCTs and can support the morphological diagnosis.
- Seminomas are the most common type of testicular GCT, seen primarily in males 30–40 years old, and most often presenting as a scrotal swelling that is large, painless, solid, and unilateral.
- Scrotal ultrasound may demonstrate characteristic findings. Seminomas typically exhibit well-defined borders and a homogeneous appearance, while nonseminomatous or mixed GCTs will more often exhibit ill-defined borders, heterogeneous appearance, and cystic components.
- The characteristic gross morphology of a seminoma is a large, bulky, and homogenous mass without necrosis or hemorrhage.

- The characteristic histological features of seminoma include large, round cells with abundant clear cytoplasm and distinct borders, surrounding lymphocyte-containing fibrovascular septa, and the occasional presence of syncytiotrophoblasts.
- Pure seminomas are associated with LDH elevation and occasional βhCG elevation, with normal AFP levels.
- Seminomas have an excellent prognosis following radical inguinal orchiectomy and may be followed by active surveillance alone or treated with adjuvant radiation and/or platinum-based chemotherapy depending on the stage.
- Embryonal carcinoma demonstrates significant anaplasia and tumor necrosis, which may be evident on gross examination.
- Yolk sac tumor demonstrates variable morphologic patterns, which resemble various extraembryonic and endodermal tissue structures and are typically associated with elevation of serum AFP.
- Teratoma recapitulates any mature or immature somatic tissue type, and serum biomarker elevations may vary depending on the tissue types present.
- Choriocarcinoma is composed of mixed trophoblastic cells and multinucleated syncytiotrophoblasts and typically demonstrates areas of hemorrhage, which may be identified on gross examination. Elevations in serum βhCG are expected, although any GCT containing syncytiotrophoblasts may be associated with serum βhCG elevations.
- The primary molecular aberration identified in GCNIS and all subtypes of GCT is duplication of the short arm of chromosome 12, resulting in i(12p). Activating mutations of KIT have also been identified in some cases of seminoma, as well as GCNIS.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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