A 28-year-old man with no significant medical history presented to his primary care provider with 4 months of progressive left-testicular enlargement. His symptoms were not associated with pain, dysuria, fever, weight loss, or recent trauma. He was sexually active only with his wife. He endorsed using condoms for contraception and denied unsafe sexual practices.

On presentation, the patient was a young, healthy-appearing man with vital signs within normal limits. Physical examination revealed a normal penis without ulceration or urethral discharge. The left testicle was grossly enlarged, compared with the right, measuring approximately 6 cm in length with an irregular shape. The right testicle was within normal limits, measuring 4 cm in length. There was no erythema of the scrotum, and both testicles were nontender to palpation. There was neither herniation noted through the inguinal rings nor palpable lymphadenopathy. Prostate examination revealed a firm, appropriately sized prostate without irregular nodularity. The results of the remainder of the physical examination were within normal limits.

1. What is the next best step in managing this patient?
   a. Prescribe a course of antibiotics and follow up in 1 week.
   b. Computed tomography of the abdomen and pelvis
   c. Testicular biopsy
   d. Scrotal ultrasound with Doppler
   e. Radical orchietomy

Although epididymitis or epididymoorchitis are common causes for testicular swelling, the predominant presenting symptoms include pain and other clinical signs of infection such as fever, rigors, and dysuria.

Further, the 4-month time course is inconsistent with acute infection. Testicular cancer must be within the differential for any patient who presents with a testicular mass. It is the most common cancer of young men, and its incidence has been increasing over time. Further, treatment results in cure in greater than 90% of patients, indicating that significant harm could be done by delaying the diagnosis and treatment. Although infection is a possibility, testicular cancer must be evaluated for before empiric antibacterial treatment.

Computed tomography (CT) of the abdomen and pelvis is clinically useful in the management of testicular cancer, but use here is premature. Computed tomography should be used after diagnosis to characterize the cancer stage, and it would be inappropriate to expose the patient to this level of radiation before, when less potentially harmful and expensive options are available. Testicular biopsy is never warranted in a patient with suspected testicular cancer as the insult may lead to tumor seeding and higher rates of local recurrence. Further, it is premature to collect tissue before imaging the mass.

Scrotal ultrasound is the next best step in evaluation of a solid testicular mass in this patient. At this time, serum tumor markers should also be collected: specifically, alphafetoprotein (AFP), beta-human chorionic gonadotropin (β-HCG), and lactate dehydrogenase (LDH). Ultrasound is a low-cost, low-risk procedure that has a high likelihood of ruling in or out testicular cancer by differentiating it from more benign conditions such as hydroceles or cysts.

Treatment of testicular cancer usually involves orchietomy of the involved testicle, but surgery is not warranted at this stage of
the work-up. The differential for testicular masses is broad, including hydrocele, varicocele, spermatocele, hematomas, and herniation. Radical orchiectomy is not a benign procedure and, as such, should be reserved for lesions that have high likelihood of malignancy. This should be determined by ultrasound, which has a high likelihood of differentiating testicular cancer from benign lesions.

Scrotal ultrasound with Doppler revealed a normally sized right testicle, measuring 4.3 x 3.1 x 2.5 cm and 7.4 mL in volume, with homogeneous echogenicity and appropriate arterial flow. The left testicle measured 6.1 x 2.7 x 3.9 cm with a volume of 50.5 mL, with conglomerate of solid heterogeneous masses with internal vascularity. Laboratory evaluation revealed the following (reference ranges provided parenthetically): hemoglobin 15.0 g/dL (13.2 to 16.6 g/dL); platelets 192 x 10^9/L (135 to 317 x 10^9/L); leukocytes 5.9 x 10^9/L (3.4 to 9.6 x 10^9/L); sodium 142 mmol/L (135 to 145 mmol/L); potassium 5.0 mmol/L (3.6 to 5.2 mmol/L); chloride 103 mmol/L (98 to 107 mmol/L); bicarbonate 27 mmol/L (22 to 29 mmol/L); blood urea nitrogen 17 mg/dL (8 to 24 mg/dL); creatinine 1.09 mg/dL (0.74 to 1.35 mg/dL); AFP 2.8 ng/mL (<6.0 ng/mL); β-HCG <0.6 IU/L (<1.4 IU/L); LDH 538 U/L (122 to 222 U/L). He subsequently had sperm cryopreservation and underwent an uncomplicated left radical orchiectomy for suspected testicular cancer. Gross specimen included a left testicle of 91 grams and 6.4 x 4.8 x 4.1 cm with an attached 14.9-cm spermatic cord. A multilobar, tan, fleshy, and necrotic mass, involving the entirety of the testicular parenchyma, was noted; margins were negative.

2. Which one of the following is most likely to be found on pathology evaluation following radical orchiectomy?
   a. Sex-cord stromal tumor
   b. Benign mass
   c. Germ-cell tumor
   d. Testicular lymphoma
   e. Secondary testicular tumor

Sex-cord stromal tumors are a type of nongerm cell tumor (NGCT). All NGCTs originate from nongerminial testicular cells, such as Leydig, Sertoli, granulosa, or theca cells. Nongerm cell tumors make up only approximately 5% of testicular tumors, making this diagnosis unlikely. Benign masses are also possible causes of testicular masses; however, they do not typically arise from the gonad itself but rather the paratesticular tissue. In general, benign lesions rarely involve the testicular parenchyma. This makes a finding of benign mass much less likely, as our patient does have testicular parenchyma involvement. Further, although benign masses present similarly to malignant lesions with testicular enlargement, gonadal tissue is more likely to become hyperplastic, and malignancy is much more common than benign growths.

The other classification of testicular tumors besides NGCTs is testicular tumors arising from germ cells, or germ-cell tumors (GCTs); these are by far the most common cause of testicular masses concerning for malignancy, excluding easily imaged findings such as hydroceles and varicoceles. They make up 95% of testicular neoplasms and include a diverse number of distinct subtypes that can be isolated or present in a heterogeneous population containing 2 or more distinct morphologies. Germ-cell tumors are further differentiated into either seminomas, nonseminomas, or a mix between the two. The most common of these is a seminoma, composed of cells that originate in germinal epithelium of the seminiferous tubules, which is found in approximately 50% of the time and is present in 1 of 5 heterogeneous GCT tumors. Nonseminomas originate from pluripotent germinal cells and include embryonal carcinomas, yolk-sac tumors, choriocarcinoma, and teratomas.

Other potential etiologies of a malignant testicular mass include testicular lymphoma, which also most commonly presents with painless unilateral testicular enlargement. However, this is predominantly a disease of the elderly and rarely presents in patients younger than 60 years of age. Further, it accounts for less than 5% of testicular masses.
malignancies, making this diagnosis unlikely. Any tissue in the body can become a host for secondary metastases. However, metastases to the testicles are extremely rare and are most commonly found incidentally on autopsy in much older patients. It would be less likely in a patient with benign examination results and normal laboratory work-up results.

The tumor pathology returned positive for seminoma with tumor extension limited to the left testis. Postorchiectomy tumor-marker work-up revealed AFP 2.4 ng/mL (<6.0 ng/mL); \(\beta\)-HCG <0.6 IU/L (<1.4 IU/L); and LDH 234 U/L (122 to 222 U/L).

3. In addition to repeat serum tumor markers, which one of the following is the most appropriate next step in management for this patient?
   a. Full-body positron emission tomography (PET) scan
   b. Chest x-ray, CT scan of abdomen and pelvis
   c. Brain magnetic resonance imaging (MRI), CT scan of chest, abdomen, and pelvis
   d. Chest x-ray, technetium 99-m skeletal scintigraphy
   e. No further imaging is necessary.

   Positron emission tomography scans should not be used in the initial evaluation of testicular cancer. The suggested imaging for testicular cancer staging is a CT abdomen and pelvis scan with contrast material, in addition to chest x-ray or CT. When deciding between chest x-ray or CT, chest x-ray is preferred for stage 1 seminoma, whereas, in nonseminomas, CT of the chest may be prioritized. Brain imaging is not warranted for testicular cancer staging. Although testicular cancer does metastasize, it commonly does so to the lymph nodes. Only very rarely does testicular cancer spread to the brain and generally only in patients with already high disease burden. Likewise, bone scan or technetium 99-m skeletal scintigraphy is not indicated in initial staging of testicular cancer. It is generally used when metastases are suspected in the bone following clinical suspicion, such as focal bone pain. Further imaging is always warranted in staging testicular cancer following orchiectomy. Although the specific pathology of this testicular cancer is limited to the left testes, this does not definitively rule out extratesticular disease.

   In this patient, CT of the abdomen and pelvis following left inguinal orchiectomy revealed neither lymphadenopathy nor metastases. Chest x-ray also revealed no thoracic lymphadenopathy or metastatic processes. As such, the patient was determined to have stage 1 disease. Treatment options were discussed with the patient, which included adjuvant chemotherapy, radiation, or surveillance. The patient elected to proceed with surveillance.

4. Which one of the following is true regarding this patient’s need for surveillance?
   a. Imaging surveillance is not required.
   b. Routine serum tumor markers
   c. Routine CT of the abdomen
   d. Routine CT of the chest, abdomen, and pelvis and serum tumor markers
   e. Routine PET scan

   This patient has an excellent prognosis with stage I disease; however, there is a significant risk of relapse within the first 5 years. Although risk of mortality is low, approximately 15% to 18% of patients with stage 1 seminoma will relapse. Therefore, surveillance is a key requirement following curative testicular cancer therapy despite the stage of the disease. Tumor markers are also integral portions of testicular cancer surveillance, although tumor markers are generally elevated in nonseminomas. Our patient did not have an elevated AFP or \(\beta\)-HCG before treatment, which is typical of pure seminomas. If AFP had been elevated, the patient would, by definition, not have a seminoma but rather a mixed or nonseminoma such as choriocarcinoma or a yolk-sac tumor. National Comprehensive Cancer Network (NCCN) guidelines specify that patients like ours, with stage IA pure seminoma, do not require serum tumor markers; however, many institutions recommend that they be collected, regardless.
The surveillance modality of choice is CT of the abdomen. Specific recommendations for stage 1 seminoma include history, physical examination, and cross-sectional imaging of the abdomen, with or without the pelvis, every 4 to 6 months for the first 2 years, followed by 6 to 12 months for the next 3 to 5 years. Chest imaging is done purely based on clinical indication. Additionally imaging after 5 years is not generally recommended, as most relapse occurs within the first 2 years of curative treatment and less than 1% of GCTs relapse after 5 years. If new disease is noted in a patient with GCT 5 years after treatment, it is important to consider new primary disease from the remaining testicle, as there is a lifetime 2% risk of contralateral GCT among patients with previous GCT. Positron emission tomography is not routinely recommended for surveillance of GCT relapse.

Surveillance imaging was started at 3 and 6 months. During the second CT scan at 6 months, the patient was found to have a newly enlarged retroperitoneal lymph node, 3.5 cm in length, which was concerning for relapse. He was treated with chemotherapy, and following 3 cycles of treatment with bleomycin, etoposide, and cisplatin, a repeat CT scan of his chest, abdomen, and pelvis revealed no residual disease. Serum tumor markers were collected and were within normal limits.

5. Which one of the following is true regarding long term health effects in this patient?
   a. He has no increased risk of developing cardiovascular disease.
   b. He has no increased risk of developing metabolic syndrome.
   c. The patient is unlikely to be able to achieve paternity.
   d. He has a higher risk of developing hypogonadism.
   e. His likelihood of developing a second malignancy is similar to that of the general population.

Cardiovascular disease is a significant risk factor that requires monitoring in long-term survivors of testicular cancer, and survivors of testicular cancer have significantly increased risk of myocardial infarction compared with the population. Risk is particularly elevated in patients with nonseminomas and those who received mediastinal radiation or combination cisplatin-containing chemotherapy. Likewise, patients with testicular cancer also have elevated risks of metabolic syndrome. Elevated risk is seen predominantly in patients treated with chemotherapy or radiotherapy and in patients with persistent hypogonadism. This is thought to be due to increased short- and long-term endothelial dysfunction caused by chemotherapy as well as the endothelial damage caused by ionizing radiation.

Although preservation of fertility should be offered to all patients with testicular cancer before initiating treatment, the likelihood that the patient will be able to achieve paternity without assistance is good. Spermatogenesis recovers to 50% and 80% at 2 and 5 years, respectively. At 15 years following treatment, there is a 85% rate of paternity. Despite the likely recovery of spermatogenesis, the patient has increased risk of hypogonadism compared with the general population. The age-adjusted risk of hypogonadism is almost 4-fold higher in survivors of testicular cancer and increases further with intensity of treatment, including those patients who received cisplatin-based chemotherapy.

Finally, survivors of testicular cancer have elevated risks of developing secondary malignancies. The largest risk is seen in patients who received combination chemoradiation, with the next largest risk seen with radiation monotherapy, then chemotherapy alone. Relative risk for secondary malignancy is approximately twice that compared with the general population. Particularly at-risk sites include the stomach, pancreas, and connective tissue.

Overall, the patient should have regular physical examinations with monitoring of weight and blood pressure. Hormonal function should be assessed regularly, with particular attention paid to signs of hypogonadism. Secondary malignancy should remain within the differential diagnosis for new patient
complaints, and physical examinations should include evaluation of lymph nodes and the contralateral testicle. This patient currently has regular-follow ups with both an oncologist and primary care physician.

**DISCUSSION**
Testicular cancer is the most common solid malignancy in young men and accounts for approximately 1% of cancers in men overall, with peak incidence between ages 14 and 44. Although specific etiologies are not well understood, there are several known risks factors for the development of testicular cancer, the most significant of which are family history and previous cryptorchidism. The risk of testicular cancer is greatly magnified in patients with male first-degree relatives who were previously diagnosed with testicular cancer, and a personal history of cryptorchidism increases risk by 5-fold.

The most common presentation of testicular cancer is a unilateral, painless, and firm testicular mass that is generally found incidentally. They can be associated with pain in a minority of patients, with as many as a one-third presenting with generalized aching pain. Acute pain is less common and only seen in approximately 10% of newly presenting patients. Metastasis is also not common at first presentation, but clinical signs that should be evaluated for anorxia, weight loss, new cough or dyspnea, lymphadenopathy, bone pain, and lower-extremity swelling.

Any male patient who presents with a new solid mass in the testes should be considered to have testicular cancer until it is proven otherwise. The prognosis of almost all testicular tumors is excellent with prompt care, and most patients will achieve cure with simple orchietomy. Scrotal ultrasound with Doppler is the imaging modality of choice, as it can easily distinguish between intrinsic and extrinsic testicular lesions. Before orchietomy, all men should be offered fertility preservation and sperm cryopreservation. Ideally, a baseline sperm count and banking should be performed before radiologic evaluation in men seeking preservation of fertility.

The large majority of testicular cancers are GCTs and requires only orchietomy of the affected testicle and close surveillance for 5 years. Advanced disease is found most commonly in the lymph nodes, followed by the lungs, which, if found, does not imply poor prognosis. Treatment for advanced disease is typically chemotherapy or radiation, and treatment remains curative in the majority of patients. Overall, 5-year rates of survival for testicular cancer exceed 90%. For chemotherapy-resistant disease, there are currently several clinical trials evaluating the efficacy of immunotherapy, which may further improve survival rates in the future.

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**REFERENCES**

**CORRECT ANSWERS:** 1. d. 2. c 3. b 4. d 5. d