A previously healthy 40-year-old man presented with a 2-day history of left leg swelling. He noticed the change 2 days previously in the anteromedial aspect of the left proximal thigh. The swelling progressed distally to involve the entire left lower extremity, accompanied by heaviness and warmth. He also reported mild left-sided abdominal pain of 1 month for which he underwent initial evaluation at another facility before being referred to Mayo Clinic for further diagnostic work-up and treatment. He denied preceding trauma, fever, diarrhea, constipation, lower urinary tract symptoms, or flank pain. He further denied insect bites, prolonged immobilization, or recent long-distance travel. He had not been taking prescribed or over-the-counter medications. He denied tobacco smoking, alcohol use, or recreational drug use.

On examination, the patient was afebrile and had a regular pulse rate of 89 beats/min, a blood pressure of 156/93 mm Hg, a respiratory rate of 18 breaths/min, and an oxygen saturation of 99% on room air. He was overall well-appearing and fully conversant. A large, nontender, firm intra-abdominal mass was palpated occupying the left lower quadrant, most of the right lower quadrant, and part of the left upper quadrant. The left lower extremity was diffusely tender and edematous. Dorsalis pedis and posterior tibialis pulses were intact bilaterally. Sensation and strength were grossly intact in all distributions. His right testicle was of normal size and texture. His left testicle was absent on palpation. The remainder of the examination was unremarkable.

Laboratory evaluation yielded the following (references ranges provided parenthetically): hemoglobin level, 13.0 g/dL (13.2 to 16.6 g/dL); platelet count, 196×10^9/L (135 to 317)×10^9/L; creatinine level, 1.17 mg/dL (0.74 to 1.35 mg/dL); activated partial thromboplastin time, 27 seconds (25 to 37 seconds). Ultrasonography revealed an extensive deep venous thrombus involving the left lower extremity from the left common femoral vein to the posterior tibial and peroneal veins with involvement of the left greater saphenous vein.

1. Which one of the following is the best next step in management for the patient’s deep venous thrombosis (DVT)?
   a. Therapeutic anticoagulation
   b. Computed tomography (CT) of the abdomen and pelvis
   c. Ultrasonography of the testicles with Doppler
   d. Computed tomography angiography of the chest
   e. Vascular surgery consultation

Given the acute extensive DVT, empirical anticoagulation should be initiated after considering risk of bleeding, which appears low in this patient. Therapeutic anticoagulation should not be deferred for diagnostic studies. The patient does need a CT of his abdomen and pelvis to evaluate the abdominal mass, and ultrasonography of the testicles is important given the absence of a left testicle; however, therapeutic anticoagulation would still be the best next step in management. A CT angiogram of the chest is not indicated unless the patient develops signs or symptoms suggestive of pulmonary embolism (PE). Therapeutic anticoagulation would both prevent further progression or embolization of the documented DVT and progression of suspected PE if present. Consultation with vascular surgery would have been of utmost importance if acute
limb ischemia or arterial thrombosis was suspected, but lack of concerning physical findings makes this unlikely.

The choice of agent is important, as the patient has an uncharacterized abdominal mass and may need further diagnostic work-up or invasive management. Use of a direct oral anticoagulant (DOAC) is an acceptable option for therapeutic venous thromboembolism (VTE) management.1-4 In contrast to warfarin, DOAC therapy (with the exception of edoxaban) does not require concomitant initiation of heparin therapy and has a shorter time to effect. Importantly, the abdominal mass could represent a malignant neoplasm. Direct oral anticoagulant therapy for VTE in the setting of cancer is preferred over warfarin therapy.2 In this case, the potential need for biopsy of the mass contributed to a decision to initiate unfractionated heparin intravenously. A weight-based intravenous unfractionated heparin infusion is an acceptable empirical option as it is fast-acting and can be held a few hours before invasive procedures if needed. Another option would be low-molecular-weight heparin (LMWH).2,3

Computed tomography of the abdomen and pelvis with intravenous contrast was then performed, revealing an acute thrombus in the left common femoral vein and complete occlusion of the left external iliac vein due to extrinsic compression by large heterogeneous soft tissue mass in the pelvis, measuring 10.8×17.3×15.2 cm. Bilateral mild hydronephrosis and mild dilatation of the left ureter was present. A smaller soft tissue mass was seen anterior to the rectum, measuring 3.0×4.6×3.7 cm, with the right seminal vesicle abutting the mass inferiorly. The left testicle could not be identified within the scrotum, whereas the right testicle appeared normal. A left nephrostomy tube was placed to relieve the hydronephrosis. Further laboratory evaluation yielded the following (references ranges provided parenthetically): serum alpha-fetoprotein (AFP) level, 4.8 ng/mL (<6.0 ng/mL); serum beta human chorionic gonadotropin (beta-hCG) level, 65 IU/L (<0.4 IU/L); lactate dehydrogenase (LDH) level, 1095 U/L (122 to 222 U/L).

2. Which one of the following diagnoses is most likely given these findings?
   a. Germ cell tumor
   b. Lymphoma
   c. Colon cancer
   d. Nephroblastoma
   e. Retroperitoneal abscess

Diagnostic considerations include germ cell tumors, lymphoma, sarcoma, colon carcinoma, and other tumors. Elevation of beta-hCG in the setting of an undescended testicle in a relatively young male patient raises suspicion for a germ cell tumor (GCT). Most patients with testicular tumors present with local testicular symptoms of pain or swelling. However, about 10% of these patients present with symptoms of metastatic disease.5 A germ cell tumor, specifically testicular cancer in the setting of cryptorchidism, is the most likely diagnosis. Lymphoma and colon cancer are reasonable possibilities given the imaging findings, but would not explain the elevation of beta-hCG. An elevated LDH can be associated with lymphoma. Nephroblastomas, also known as Wilms tumors, are almost exclusively seen in childhood. A retroperitoneal or pelvic abscess is less likely given the absence of leukocytosis, fever, or significant tenderness on examination.

Tissue biopsy was planned for the next day. The results of CT-guided biopsy of the pelvic retroperitoneal mass confirmed the diagnosis of advanced seminoma. Computed tomography of the chest revealed scattered subsegmental pulmonary emboli but no evidence of metastatic disease in the thorax.

3. Which one of the following is the most appropriate next step of this patient’s management strategy?
   a. Etoposide and cisplatin, with or without bleomycin
   b. Orchiectomy
   c. Retroperitoneal lymph node dissection (RPLND)
d. Discussion of fertility preservation

e. Radiation of the mass

Chemotherapy is indicated, but fertility preservation should be discussed first as the drugs may lead to infertility. With this bulky seminoma arising from an undescended intra-abdominal testicle, orchietomy is technically difficult. If the testicle were in the scrotum and a mass identified, then radical inguinal orchietomy would have been the preferred approach over biopsy of the lymph nodes as orchietomy would be both diagnostic and therapeutic. The testicle harboring GCT typically requires removal as it is poorly penetrated by chemotherapy and thus serves as a sanctuary site for cancer. Retroperitoneal lymph node dissection is usually reserved for patients with residual masses after completion of chemotherapy; the decision about whether to pursue RPLND requires a multidisciplinary opinion. In this case of viable seminoma with bulky lymph nodes and elevated beta-hCG, chemotherapy should be administered first. Importantly, testicular cancer treatment can affect fertility. Discussions on fertility preservation should occur early in the treatment planning phase, before initiating chemotherapy, to allow time for scheduling interventions and avoiding delays in initiating cancer-directed therapy. The decision to wait for evaluation by a reproductive endocrinology specialist needs to be individualized. In most cases, this evaluation is possible; however, if imminent risk to organ function is present, emergent chemotherapy may be necessary. On occasion, and only in pure seminoma, radiation can be used if the retroperitoneal lymph node mass is small.6

Counseling was provided on fertility preservation, with the decision made to forgo sperm banking as the patient already had children. The benefits and risks of anticipated chemotherapy were discussed. Critical risks of bleomycin therapy include pneumonitis and pulmonary fibrosis. Assessing baseline pulmonary status through history, examination, and pulmonary function testing was indicated. Renal insufficiency, hypomagnesemia, neuropathy, VTE, and ototoxicity were explained as adverse effects associated with cisplatin therapy. The patient expressed understanding of the treatment options and was initiated on bleomycin, etoposide, and cisplatin, with supportive measures including intravenous fluids and antiemetic therapy. Finally, anticoagulation for DVT/PE was discussed. The patient expressed interest in pursuing oral anticoagulation over an injectable form.

4. On the basis of the patient’s preferences, which one of the following is the most appropriate regimen for outpatient anticoagulation management of VTE?

a. Enoxaparin for 6 months
b. Fondaparinux for 6 months
c. Apixaban for 2 months
d. Rivaroxaban for 6 months
e. Warfarin for 2 months

Dalteparin is the only LMWH with US Food and Drug Administration approval for extended therapy to prevent recurrent thrombosis in patients with cancer. However, in the United States where dalteparin is not widely used, enoxaparin, usually at the dose of 1 mg/kg twice daily, seems to be an effective alternative in malignancy-associated VTE. Fondaparinux may also be used, especially if a history of heparin-induced thrombocytopenia is present. However, neither is an appropriate option in this case as the patient requested that an oral alternative be provided. It is recommended that DOAC therapy, when used for VTE in cancer, be maintained for at least 6 months, until there is no evidence of malignancy, and until cancer-directed therapy is completed. Apixaban would have to be prescribed for 6 months. Based on duration of treatment needed as well as patient preference, the most appropriate listed regimen is rivaroxaban 20 mg daily for 6 months after the 21 days of initiation therapy at 15 mg twice daily. Warfarin is not approved for use in VTE in malignancy.

For years, LMWH injections had been considered the first-choice agents in malignancy-associated VTE. Multiple
DOACs including rivaroxaban have now been found to be at least noninferior to LMWH.\textsuperscript{1,2,7} Patient preference for noninjectable therapy often results in using DOACs. When outcomes of recurrent VTE and major bleeding are examined, DOACs are well tolerated and safe. They do not require bridging, except for edoxaban. Oral apixaban was notably found to be noninferior to dalteparin with no associated increased risk of major bleeding in a recent study.\textsuperscript{1,2,4,7}

The patient was discharged on rivaroxaban therapy for 6 months. He completed chemotherapy with normalization of his tumor markers. Follow-up imaging revealed reduction of the pelvic mass to $6.5 \times 5.2$ cm. The need for RPLND will be determined on the basis of ongoing follow-up by the multidisciplinary genitourinary tumor board.

5. In addition to GCT markers, which one of the following laboratory test results should be monitored as part of the patient’s long-term care?
   a. Carcinoembryonic antigen
   b. Prostate-specific antigen
   c. Liver function test
   d. Thyroid-stimulating hormone
   e. Fasting glucose

In the survivorship period, it is not recommended to monitor tumor markers that are not related to GCT, such as carcinoembryonic antigen and prostate-specific antigen, outside of established age-appropriate health screening. Liver function tests may be considered for individuals with metastatic involvement in the liver but are not otherwise indicated as part of follow-up. Thyroid-stimulating hormone is similarly not specifically followed for patients with testicular cancer.\textsuperscript{8} GCT survivors are at a significantly increased risk of developing metabolic syndrome and cardiovascular disease as long-term complications.\textsuperscript{9} Therefore, routine evaluation of fasting glucose levels, lipid panels, blood pressure, and weight is important.

Evaluation for metabolic syndrome in testicular cancer survivors is a vital role of the primary care physician, as 1 in 5 is predicted to develop the condition. A combination of elevated glucose, lipids, blood pressure, and/or weight characterizes metabolic syndrome, which is associated with an increased risk of developing type 2 diabetes mellitus and cardiovascular disease. Platinum-based chemotherapy in testicular cancer management has been associated with a higher prevalence of hypertension, increased low-density lipoprotein, and diabetes mellitus.\textsuperscript{7} Monitoring of heart health is essential as post-chemotherapy survivors are at a higher risk for coronary artery disease and myocardial infarction. Primary care professionals should initiate intensive lifestyle management and medications as appropriate in patients at risk. The patient in this case was found to have persistent hyperglycemia following oncological treatment, and he established as a patient with the resident primary care clinic for further management.

DISCUSSION
Testicular cancer is the most common and most curable solid tumor in male patients aged 15 to 35 years, with a 5-year survival rate of more than 97% in early-stage seminoma.\textsuperscript{10} Many patients present with a painless, firm testicular mass. Given our patient’s cryptorchidism, the palpable retroperitoneal mass in conjunction with unilateral leg swelling—indicative of VTE and extrinsic vascular and lymphatic compression—became the telling physical presentation finding. Approximately 10% of patients with GCT tumor present with extratesticular signs and symptoms secondary to metastatic disease.\textsuperscript{5}

Risk factors for testicular cancer include cryptorchidism, history of infertility, human immunodeficiency virus, and family history of testicular cancer. There is no recommended screening or surveillance testing for testicular cancer outside the clinical and self-examination of the testicles if there is high suspicion. If a testicular mass is suspected, the physical examination should begin with the unaffected testis and scrotal area for comparison, carefully pressing the contents between the thumb and the second
and third digits of the examining hand on each side. In cases of concurrent hydroceles, which may obscure the testicular examination, ultrasonographic imaging can be helpful in uncovering underlying malignancies. Inspection of the lymph nodes, chest (gynecomastia), and abdomen should also be performed to assess for retroperitoneal or other visceral involvement.

Initial diagnostic laboratory evaluation includes measuring serum tumor markers and chemistries and obtaining a testicular ultrasound. The patient should then be referred to urology. Transscrotal biopsy of a mass should not be performed because of the risk of seeding the hemiscrotum. If the mass is clinically suspicious for testis cancer, the urologist will usually advise orchiectomy as the next step. Scrotal masses that are solid rather than cystic or fluid-filled, and intratesticular rather than extratesticular, have a higher likelihood of representing malignancy. Gonadal function may be considered for baseline measurement. Serum tumor marker levels, which include beta-hCG, LDH, and AFP, serve as an important guide for the diagnosis of specific GCTs. Beta-hCG can be elevated in both seminoma and nonseminoma. It is elevated in approximately 20% of patients with pure seminoma. If the beta-hCG level is elevated beyond 1000 IU/L, a diagnosis of nonseminoma is more likely. The serum AFP level is never elevated in patients with pure seminoma. Serum LDH is neither a sensitive nor a specific indicator of GCT as it can be elevated because of tissue injury. However, serum LDH contributes to the determination of prognostic stage groups, with elevated levels being commonly associated with high tumor burden. Rising levels of LDH may be an early biochemical indicator of testicular cancer recurrence. Nonseminomatous GCT can contain elements of seminoma, mixed with nonseminomatous histologies, which include yolk sac tumor, choriocarcinoma, embryonal carcinoma, and teratoma. Distinguishing between seminoma and nonseminoma is essential for establishing the appropriate treatment strategy.6,8

Primary care physicians play a key role in monitoring of complications after the treatment of GCT. Long-term complications include cardiovascular disease, metabolic syndrome, kidney disease, peripheral neuropathy, chronic pulmonary toxicity, secondary malignancies, hearing loss, and sexual dysfunction. In particular, primary care physicians should consider follow-up pulmonary function testing for patients in whom bleomycin was used for therapy if the patient has persistent clinical signs such as rales or symptoms such as cough or dyspnea.

The risk of secondary solid tumors is also increased in patients treated for testicular cancer, including bladder cancer, pancreatic cancer, gastric cancer, and leukemia. The lifetime risk of developing GCT in the contralateral testicle is approximately 1%. In select situations, radiation therapy is used for pure seminomas. Survivors who were treated with radiation therapy are at increased risk of soft tissue sarcomas and other solid tumors, typically years after treatment.6 Chemotherapy and radiation therapy increases the risk of myelodysplastic syndrome and secondary acute leukemia after treatment of testicular cancer.11 Therefore, despite lack of definitive data on the utility and cost-effectiveness of routine complete blood count monitoring, clinicians should consider secondary leukemia and myelodysplastic syndrome in the context of worsening cytopenias in the testicular cancer survivor.

Finally, survivors of testicular cancer are at risk for significant psychological and sexual dysfunction, with more than a quarter of patients reporting impairments in these areas or other somatic effects. Anxiety is particularly prevalent. Treatment-related infertility may further exacerbate these issues. As such, mental health assessment is an important component of care in testicular cancer survivors.12 Given that most men with testicular cancer are diagnosed and treated at a young age with prolonged long-term survival, survivorship care tailored to the risk factors specific to this population is essential to optimizing longevity and quality of life.
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REFERENCES


CORRECT ANSWERS: 1. a. 2. a. 3. d. 4. d. 5. e.