A 57-year-old woman with no significant medical history presented to the emergency department (ED) with acute onset right-sided weakness, sensory loss, and new word-finding difficulties. Her only home medication was a daily multivitamin. She was in her normal state of health until 3 weeks before admission when she developed episodes of weakness and decreased sensation of her right hand. She was evaluated locally and her work-up, including a head computed tomography (CT), was reportedly unrevealing; so she was asked to follow up with her primary care physician as an outpatient. Her symptoms progressively worsened however, and she developed new word-finding difficulties, which prompted her husband to bring her to the ED. There was no loss of consciousness or involuntary movements. There was no family history of strokes or seizures. She was alert, awake, and oriented to time, place, and person. Vital signs were stable. Pertinent physical examination findings included fluent aphasia with frequent paraphasic errors, difficulty with word finding and repetition, no overt dysarthria, right pronator drift, right upper extremity pyramidal distribution weakness, and sensory loss in the right arm. Cardiopulmonary and abdominal examinations were unremarkable.

Laboratory studies revealed the following results (reference ranges within parentheses): hemoglobin level, 9.1 g/dL (12.0 to 15.5 g/dL); white blood cell count, 9.2 × 10^3/L (3.5 to 10.5) × 10^3/L; platelet count, 163 × 10^3/L ((150 to 450) × 10^3/L); and point of care testing glucose level, 106 mg/dL (70-100 mg/dL). Stroke laboratory results included a normal hemoglobin A1c level of 4.9 g/dL, and a lipid panel revealed a total cholesterol level of 174 mg/dL (desirable < 200 mg/dL) and a low-density lipoprotein cholesterol level of 106 mg/dl (desirable <100 mg/dl). Other values for a metabolic panel, including renal function, were within the reference range. An electrocardiogram revealed normal sinus rhythm. Noncontrast CT of the head found no evidence of ischemia or hemorrhage.

1. Which one of the following tests would provide the highest diagnostic yield in this patient?
   a. Magnetic resonance imaging of the brain
   b. Transesophageal echocardiography
   c. Carotid artery duplex ultrasound
   d. Electroencephalography
   e. Electromyography

Although noncontrast head CT is often performed first to assess for hemorrhage or large infarct, magnetic resonance imaging of the brain should be considered in this patient with suspected stroke and unrevealing head CT. Magnetic resonance imaging is more sensitive in this case and can help further identify the type and distribution of strokes in addition to guiding further work-up for a source. Obtaining a transesophageal echocardiogram in this patient now would be premature, as it is unclear yet if she has a stroke of cardioembolic origin. Similarly, carotid artery duplex ultrasound might be helpful later if an atherothrombotic stroke is suspected. Electroencephalography might have some value, as seizures are important stroke mimics that frequently present with transient hemiparesis and altered consciousness. But our patient’s intact mental status and evolving neurological deficits are less consistent with a focal seizure. Electroencephalography can be considered if further imaging is inconclusive for stroke. Electromyography can be helpful in various...
muscular, neuromuscular, and peripheral nerve diseases. In this patient however, it is not indicated given the presence of focal neurological deficits with aphasia, suggesting a cerebrovascular accident.

Magnetic resonance imaging of the brain revealed multiple acute and subacute infarcts scattered throughout the cerebral and cerebellar hemispheres and multiple vascular territories. Computed tomography angiography of the head and neck was negative for thrombosis or occlusion. Cardiac monitoring revealed no atrial fibrillation, and transthoracic echocardiogram was normal with no vegetations or masses.

2. Given what we know so far, which one of the following is the most appropriate therapy to prevent future strokes in this patient?
   a. Abciximab
   b. Warfarin
   c. Apixaban
   d. Triple antiplatelet therapy (aspirin, clopidogrel, and dipyridamole)
   e. Aspirin

   In addition to risk factor modification, and as the stroke etiology is being determined, it is important to determine the pharmacological regimen a patient should begin for secondary stroke prevention. Abciximab is an intravenous glycoprotein IIb/IIIa inhibitor that has no role in this situation. Even when tested in the treatment of acute ischemic stroke, it was associated with a significant risk of intracranial hemorrhage without a measurable improvement in death or disability.6 Anticoagulation with warfarin or a direct oral anticoagulant (apixaban) is not currently indicated for secondary prevention in our patient, but rather in those with cardiac sources of embolism such as atrial fibrillation.6 Triple antiplatelet therapy should not be administered for secondary prevention in patients with noncardioembolic ischemic stroke given the lack of benefit and the significant increase in bleeding risk.4 Despite some recent literature questioning the role of aspirin in primary prevention, its benefit in secondary prevention is proven and supported by several studies that reported a significant reduction in the risk of recurrent stroke, so it is the correct medication to initiate here.5

   Appropriate outpatient follow-up was arranged, and the patient was discharged on 81 mg of aspirin daily and 40 mg atorvastatin daily. Seventeen days later, she was readmitted to the hospital after presenting to the ED with worsening aphasia and hypoxia. Computed tomography angiography of the head and neck revealed new occlusion of the left M2 branch of the middle cerebral artery. Computed tomography of the chest with intravenous contrast revealed a large saddle pulmonary embolus, which extended from the main pulmonary artery into the right and left pulmonary arteries. Additional pulmonary emboli were visualized extending into the bilateral lower lobe segmental and subsegmental pulmonary arteries, interlobular artery, and right upper lobe segmental pulmonary artery. There was no evidence of right heart strain. Extensive deep venous thrombosis of the bilateral lower extremities was found on ultrasound as well. Complete blood count and peripheral smear were normal.

3. Which one of the following laboratory tests would be most helpful to narrow the differential diagnosis of this patient’s hypercoagulability?
   a. D-dimer
   b. Antithrombin activity
   c. Activated protein C and S levels
   d. Antiphospholipid antibody levels
   e. Erythrocyte sedimentation rate

   D-dimer is a fibrin degradation product that can be helpful in the initial detection of a thrombus. It has low specificity, however, and does not assist in narrowing the differential after the diagnosis is made, as most patients will have an elevated value. Antithrombin, protein C, and protein S are natural anticoagulants, and their deficiency is associated with inherited thrombophilia. Acute thrombosis can reduce the plasma concentrations of antithrombin, protein C, and protein S; hence, testing should be delayed.
until the patient recovers and is no longer receiving an anticoagulant. Antiphospholipid syndrome is the most common cause of acquired thrombophilia and is characterized by arterial or venous thromboembolic events. Antiphospholipid antibodies are a key diagnostic component of this syndrome, so they can help narrow the differential here. Elevated titers test should be repeated after 12 weeks. Erythrocyte sedimentation rate lacks specificity, so it would not help narrow the differential diagnosis in this patient.

Antiphospholipid antibodies were not detected in our patient. On further questioning, she had abdominal bloating, early satiety, and vague pelvic pain. A CT scan of the abdomen and pelvis exhibited a 10.5 cm right ovarian mass with multiple metastatic peritoneal implants, the largest of which measured 1.9 cm. Metastatic adenopathy vs additional implants along a branch of the superior mesenteric vein, multiple bilateral renal infarcts, and a splenic infarct were also observed. Ultrasound-guided biopsy of the large pelvic mass exhibited clear cell carcinoma.

4. Which one of the following is the best anticoagulation option to initiate in this patient?
   a. Aspirin 325 mg
   b. Enoxaparin
   c. Warfarin
   d. Edoxaban
   e. Dabigatran

Aspirin, even at a dose of 325 mg, has no role in cancer-associated venous thromboembolism (VTE). Enoxaparin remains a first line agent in these cases and has been found to be superior to warfarin. Treatment should continue for at least 6 months regardless of cancer type, and physicians should consider continuing further if the patient has active cancer with no significant bleeding complications. Edoxaban and dabigatran are direct oral anticoagulants, and although edoxaban has more evidence in cancer-associated VTE, they both require parenteral anticoagulation to be administered and overlapped for few days before their initiation; hence, they cannot be used here as initial anticoagulants.

Our patient began receiving enoxaparin 1.5 mg/kg daily and discharged with oncology follow-up. Three weeks later, she again presented to the ED with fever and melena. Anticoagulation was held, and repeated CT of the abdomen and pelvis found an increase in size of the malignant mass with erosion of a loop of the distal ileum into the mass, matting of additional loops of bowel against the mass, likely developing abscess against the superior aspect of the mass, and increasing size of peritoneal nodules.

5. Which one of the following is the most appropriate next step in the management of this patient?
   a. Surgical debulking
   b. Initiation of chemotherapy
   c. Initiation of radiation therapy
   d. Initiation of immunotherapy
   e. Palliative medicine consult

The patient is not a candidate for debulking surgery, given her comorbidities of hypercoagulability with recent bilateral pulmonary emboli and strokes, diffuse carcinomatosis with contained bowel perforation, and direct communication between bowel and tumor. Advanced stage ovarian clear cell carcinoma is associated with a poorer prognosis compared with other histological subtypes and is relatively chemotherapy resistant. There is also a potential infection in this patient, so now is not the right time to initiate chemotherapy. Radiation therapy has a limited role here, as it is primarily used as an adjuvant therapy after surgery or chemotherapy. Immunotherapy currently has no role as a first line treatment in these cases. It would be wise to consult palliative medicine in this patient, as early palliative care interventions can substantially improve quality of life and lower symptom intensity as compared with standard cancer care alone. Palliative medicine was consulted and multidisciplinary goals of care discussions were held. Eventually, the patient and her family decided to pursue a palliative care approach, with emphasis on good symptom management. She was discharged home with hospice.
DISCUSSION

A hypercoagulable state is a common complication of malignant neoplasm that represents the second most frequent cause of death in patients with cancer after infection. The multifactorial etiology behind this state can explain why it occurs in several types of cancers affecting different regions of the body. Tumor cells secrete procoagulant substances and inflammatory cytokines, which ultimately increase the risk of clot burden. Additionally, host tissues have been found to express procoagulant activity in response to tumor burden. Other extrinsic factors that promote thrombus formation in patients with malignant neoplasm include bed rest, infection, surgery, and chemotherapy. Furthermore, nonspecific factors such as inflammation and abnormal protein metabolism can lead to increased thrombus promotion.

There is evidence to indicate that thrombotic episodes may precede the diagnosis of a malignant neoplasm by months or even years. These episodes can present in various ways including arterial thrombosis, idiopathic deep vein thrombosis, marantic endocarditis, migratory superficial thrombophlebitis (Trousseau syndrome), disseminated intravascular coagulation, or thrombotic microangiopathy.

The American Society of Clinical Oncology and the National Comprehensive Cancer Network endorse a risk stratification tool known as the Khorana score, which was developed in 2008. This tool was developed to assess the risk of venous thromboembolic events in ambulatory patients with cancer receiving chemotherapy. The Khorana score uses tumor type and prechemotherapy laboratory parameters such as platelet count, hemoglobin level, leukocyte count, and body mass index (calculated as the weight in kilograms divided by the height in meters squared) to risk stratify these patients. A score of 0 confers low risk of VTE; 1 to 2 points indicates an intermediate risk; and those with a score of greater than 3 have a high risk of VTE. A recent meta-analysis evaluated the use of the Khorana score over a 10-year period and revealed that it can aid clinicians in identifying patients at high risk for VTE.

In the latest 2019 guidelines, the American Society of Clinical Oncology recommends initiating thromboprophylaxis with rivaroxaban, apixaban, or edoxaban in those with a Khorana score of 2 or greater.

It is important to recognize that although venous and arterial thromboembolism is a common complication of cancer, it can also be a marker of an occult malignant neoplasm as exhibited by this case. A large-scale cohort study was conducted on the association of VTE and subsequent diagnosis of cancer and found an increased risk in various cancer types during the first year after VTE diagnosis.

This study also reported the higher risk of cancer in patients younger than 60 years and those with recurrent episodes of VTE. Despite this information, extensive work-up to search for an undiagnosed malignant neoplasm is not recommended. Multiple studies have reported that patients should be evaluated for an underlying cancer only if they have signs/symptoms suggestive of an underlying cancer or recurrent idiopathic thrombosis. At this time, screening all patients with VTE and no risk factors for the development of a malignant neoplasm is not cost-effective and causes unnecessary psychological stress. However, it is our duty to ensure that patients are up to date regarding age- and sex-specific cancer screening (colon, breast, cervix, and prostate) as per national recommendations.

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