A 58-year-old woman presented to the emergency department with a 5-month history of worsening cough and new-onset exertional dyspnea. She reported back pain, palpitations, recent sinus congestion, subjective fevers, poor appetite, and night sweats. Her past medical history included hypertension and hyperlipidemia. The patient was taking amlodipine, lisinopril, and simvastatin and was recently prescribed levocetirizine for sinus congestion. She resided in Kansas but had been traveling to and from Arizona, with her last trip being 23 days ago on a 19-hour car trip. She had no recent surgical procedures, history of pulmonary embolism (PE), deep venous thrombosis (DVT), or active malignant disease. She was a never smoker, had no family history of malignant disease, and has 2 children.

On presentation, the patient had a temperature of 37.8°C with a heart rate of 110 beats/min, blood pressure of 164/83 mm Hg, respiratory rate of 20 breaths/min, and oxygen saturation on room air of 92%. Physical examination was notable for an uncomfortable woman with a cough. There was no evidence of jugular venous distention or peripheral edema, and heart sounds were normal. Pulmonary examination showed cough exacerbated by deep inspiration with no wheeze or crackles. No rash or lymphadenopathy was noted.

In the emergency department, laboratory examination revealed the following (reference ranges provided in parentheses): hemoglobin, 13.2 g/dL (11.6 to 15.0 g/dL); hematocrit, 39.1% (35.5% to 44.9%); platelets, 187 × 10⁹/L (157 to 371 × 10⁹/L); white blood cell count, 14.4 × 10⁹/L (3.4 to 9.6 × 10⁹/L); bicarbonate, 21 mmol/L (22 to 29 mmol/L); creatinine, 1.03 mg/dL (0.59 to 1.04 mg/dL); high-sensitivity troponin, 258 ng/L (<10 ng/L); and D-dimer, 20,943 ng/mL (<500 ng/mL). The electrocardiogram revealed sinus tachycardia with Q-wave and T-wave changes in the inferior leads.

1. Based on this patient’s findings, which one of the following is the most likely diagnosis?
   a. Heart failure
   b. Acute coronary syndrome (ACS)
   c. PE
   d. DVT
   e. Community-acquired pneumonia

The patient has hypertension, which can lead to diastolic dysfunction and heart failure; however, she had no clinical evidence of volume overload (eg, S3/S4, elevated jugular venous pressure, or lower extremity edema). For a patient who presents to the emergency department with dyspnea, an acute coronary event should be ruled out, especially with risk factors such as hypertension and hyperlipidemia because of the morbidity and mortality associated with a delayed diagnosis. Although the patient did not present with symptoms associated with ACS, such as typical chest pain, it is essential to rule out ACS with cardiac biomarkers and an electrocardiogram. Although the patient’s high-sensitivity troponin level was elevated, this was in conjunction with elevated D-dimer. Although a PE can cause an elevated troponin level because of right ventricular strain, an acute coronary event would not have the same reciprocal change in D-dimer.¹ The patient’s Q-wave and T-wave changes in the inferior leads are nonspecific in differentiating ACS from PE as these findings can be seen in both disease states.²,³ In addition, evaluation of
non-ST-segment elevation myocardial infarction typically requires serial electrocardiograms and serum troponin determinations during several hours, with a PE being able to be quickly excluded in the interim. PE should be ruled out before a cardiac work-up (eg, stress testing) to avoid unnecessary hemodynamic demand unless there is evidence of ST-segment elevation myocardial infarction, which would require immediate coronary reperfusion therapy. In this clinical scenario, it is crucial to rule out a potentially life-threatening PE, given symptoms of exertional dyspnea, tachycardia, recent 19-hour car trip, and elevated D-dimer. Although the patient had no clinical evidence of DVT (eg, unilateral edema, erythema, or pain), presence of DVT on evaluation would imply PE. A negative test result, however, would not be helpful. Although bacterial community-acquired pneumonia can elicit symptoms of dyspnea and subjective fevers, the diagnosis is less likely because of the extended time course of her symptoms. In the emergency department, the patient did receive empirical antibiotic coverage with ceftriaxone and azithromycin; however, antibiotics were discontinued within 48 hours. In addition, she underwent further investigations confirming a PE.

2. Which of the following would be the next best step in the diagnostic evaluation of this patient?
   a. Computed tomography pulmonary angiography (CTPA)
   b. Echocardiography
   c. Chest radiography
   d. Lower extremity ultrasound
   e. N-terminal pro-B-type natriuretic peptide (NT-proBNP)

   All these tests would be helpful in assessing a patient with similar symptoms to reliably exclude infection or a cardiac cause, given the laboratory investigations described. Given the high pretest probability of PE with the markedly elevated D-dimer in conjunction with the patient’s clinical features, a PE must first be excluded. The “gold standard” for diagnosis of a PE is CTPA, which enables direct visualization of the pulmonary vasculature for evidence of thrombi. A CTPA examination was indeed performed and showed multiple subsegmental pulmonary emboli involving the right upper lobe, right lower lobe, and left lower lobe pulmonary arteries, with occlusive thrombus involving the posterior right lower lobe segmental pulmonary artery. Interestingly, CTPA also showed a cavitary 2.1-cm nodule within the left lower lobe with surrounding consolidation as well as mediastinal lymphadenopathy. Lung biopsy later confirmed pulmonary adenocarcinoma. Computed tomography as well as echocardiography can assess for evidence of right ventricular strain because of elevated pulmonary vascular pressure; however, echocardiography cannot reliably exclude the presence of pulmonary emboli. A chest radiograph does not provide adequate resolution to identify a PE but can provide evidence to support a diagnosis of PE, such as enlarged pulmonary artery (Fleischner sign), wedge-shaped infarct at the lung periphery (Hampton hump), or reduced regional blood flow (Westermark sign) due to presence of thrombi within the pulmonary vessels. Lower extremity ultrasound to evaluate for the presence of DVT in the setting of D-dimer can be considered, although if lower extremity ultrasound does indeed confirm thrombosis, without CTPA, we still have not confirmed the diagnosis of PE. However, the ultrasound findings may potentially be important if the patient has any contraindications to systemic anticoagulation when inferior vena cava filter placement needs to be considered and may be helpful as the first screening step if the patient has known allergy to contrast material and time is needed for premedication. Troponins and NT-proBNP can be elevated in patients with PE and are related to right ventricular strain; however, both these serum markers can be elevated in many other conditions as well. As in our patient’s case, serum troponin was significantly elevated with evidence of right ventricular strain on CTPA indicated by flattening of the intraventricular septum.
3. Which **one** of the following options is the **most appropriate** initial management for this patient?
   a. Catheter-directed thrombolysis
   b. Unfractionated or low-molecular-weight heparin
   c. Warfarin
   d. Aspirin and clopidogrel
   e. Diuresis

   In patients who present with evidence of PE and hemodynamic compromise, systemic thrombolysis (eg, tissue plasminogen activator) or, if systemic thrombolysis is contraindicated, mechanical or pharmacomechanical reperfusion therapy (eg, surgical embolectomy or percutaneous catheter-based therapies) can be used. Our patient presented to the hospital without evidence of hemodynamic compromise, and parenteral therapy can be started with unfractionated or low-molecular-weight heparin. She may later be transitioned to warfarin or a novel oral anticoagulant. Aspirin and clopidogrel are used in the treatment of ACS and have no place in the acute management of PE. The patient did not present with volume overload, making diuresis incorrect. In fact, diuresis would further decrease preload, which may lead to life-threatening hypotension, depending on the right ventricular response to the burden of PE. Our patient did not receive any diuretics on admission, and she had no evidence of volume overload, pulmonary edema on thoracic imaging, or history of left ventricular dysfunction. However, on admission, she received high-intensity parenteral heparin for treatment of her pulmonary emboli.

4. Which **one** of the following will provide the **best** risk stratification marker on the severity of PE?
   a. Hemodynamic assessment (blood pressure)
   b. Echocardiography
   c. Serum lactate
   d. Troponin
   e. NT-proBNP

   The best risk stratification marker is hemodynamic instability (or blood pressure), which clearly identifies patients with high short-term mortality. There are other risk stratification options, including use of the Pulmonary Embolism Severity Index or the simplified version, bedside echocardiography, and biologic markers, including troponins and brain natriuretic peptide. Prior studies suggested that in low-risk PE, elevated troponin is associated with a higher mortality rate (30-day or hospitalization) at 3.8% compared with patients with right ventricular dysfunction (1.8%). Echocardiography does not improve prognostication in patients with low-risk acute PE who lack other clinical features of right ventricular dysfunction but does have a role in higher risk patients, although the therapeutic benefit of echocardiography in hemodynamically stable patients is still unclear. In the case of the patient described, transthoracic echocardiography showed right ventricular strain without right ventricular dysfunction. Echocardiography also showed a right ventricular thrombus as well as valvular vegetation on the aortic valve. Right ventricular thrombi typically occur in hemodynamically compromised patients and are a poor prognostic indicator in hemodynamically stable patients. Acute kidney injury and elevated serum lactate may be present in obstructive shock secondary to a PE; however, they are nonspecific findings in other forms of shock (eg, distributive shock in sepsis). Serum biomarkers such as troponin and brain natriuretic peptide have been shown to indicate right ventricular strain and correlate to poor-prognostic indicators. Although our patient’s blood cultures remained negative, the findings of valvular vegetation on transthoracic echocardiography prompted further evaluation with transesophageal echocardiography, confirming a lesion on the aortic valve with mild to moderate aortic valve regurgitation.

5. What would be the **most appropriate** next step in managing the aortic valve lesion found on transesophageal echocardiography?
   a. Antimicrobial therapy
   b. Coccidioidomycosis serology
c. Surgical aortic valve replacement  
d. Corticosteroids  
e. Anticoagulation

In the setting of a known valvular lesion, an infective cause of the patient’s aortic valve vegetation needs to be evaluated with at least 3 sets of blood cultures. In the case of our patient, multiple sets of negative blood cultures with biopsy-confirmed pulmonary adenocarcinoma suggested nonbacterial thrombotic endocarditis (NBTE), with no need to initiate antimicrobial therapy. Cocci dioidomycosis would be a rare cause of infective endocarditis, with a bacterial etiology having to be ruled out first. Patients with NBTE may need to be evaluated for surgical repair if evidence of severe valvular dysfunction, large vegetation, or recurrent embolization exists despite the use of anticoagulation. The patient was evaluated by the cardiothoracic surgery service and no surgical intervention was offered as she had no significant valvular dysfunction and was a poor surgical candidate, given her clinical comorbidities. Another treatment option for management of NBTE is the use of corticosteroids. Corticosteroids aid in improving healing of valvular lesions but can also accelerate fibrosis, leading to cardiac valve dysfunction. Currently, the data supporting the use of corticosteroids in NBTE are inconclusive. Because of the risk of systemic embolization, patients with NBTE should be prescribed anticoagulation; most published literature supports use of low-molecular-weight heparin. Warfarin should not be used in patients with NBTE as it has not been shown to prevent thromboembolic events. Our patient had multiple embolic events to the brain, kidneys, spleen, and left lower extremity and was prescribed anticoagulation to prevent recurrent embolization as well as to treat her pulmonary emboli.9

DISCUSSION
The Centers for Disease Control and Prevention report the incidence of venous thromboembolism to be approximately 1 or 2 per 1000 individuals, with approximately one-quarter of individuals presenting with sudden death.10 Pulmonary emboli typically arise from the lower extremity venous system as a result of predisposing risk factors (eg, recent surgery, immobilization, malignant disease) or possibly because of underlying thrombophilia.1 The most common clinical symptom of PE on presentation is dyspnea (73%); the next most common symptoms are pleuritic pain (66%) and cough (37%).2 Risk of potential PE can be calculated using clinical decision tools such as variations of the Wells criteria and Geneva score. These tools aid in estimating pretest probability and appropriate use of investigations. Currently, computed tomography angiography is used for diagnosis of PE in those patients with high pretest probability. In those with low pretest probability of PE, D-dimer, a fibrin split product, can be used to aid in ruling out PE. However, because of the low specificity of the test and growing use of D-dimer, the PE rule-out criteria were developed, which aid in differentiating the need for using D-dimer in very low risk patients.11

Management of PE is based on risk stratification, which is essentially determined by the presence of hemodynamic instability. Hemodynamic compromise derives from the effect of right ventricular dysfunction, which is best evaluated by imaging (eg, echocardiography); however, serum troponin and NT-proBNP are measures of myocardial stretch and strain on the right ventricle. Fortunately, most patients present to the hospital hemodynamically stable and can be further stratified using clinical tools such as the Pulmonary Embolism Severity Index.8 In hemodynamically stable patients, therapy is initially started with a parenteral anticoagulant such as heparin or low-molecular-weight heparin. Outpatient management is typically done with vitamin K antagonist or newer direct oral anticoagulants.1 Duration of anticoagulant therapy is commonly decided on the basis of the underlying cause of the PE. However, for patients with active malignant disease, the duration of therapy is typically lifelong based on the most recent CHEST guidelines.12 This is
because active malignant disease is a known risk factor for venous thromboembolic events, with a 15% to 20% recurrence rate without anticoagulant therapy. The optimal duration of anticoagulant therapy for a patient with active cancer with isolated distal DVT not associated with surgery is not known; however, management has been like treatment of cancer patients who have experienced proximal DVT, which is lifelong anticoagulation. There is an ongoing trial to study whether the intensity of anticoagulation therapy can be safely lowered after the initial 6 to 12 months to achieve the same benefit effects to prevent further thromboembolic events (NCT03080883).

For hemodynamically unstable patients, initial supportive measures include respiratory (supplemental oxygen to maintain saturations above 90%) and hemodynamic (eg, intravenous fluids or vasopressors) support. Reperfusion therapy for hemodynamically unstable patients can involve systemic thrombolysis, embolectomy, or catheter-directed modalities. Typically, the last options are used in patients with a contraindication to thrombolysis. Several features can be used to assess prognosis. One of those features is evidence of a thrombus in the right ventricle; interestingly, this is more commonly seen in patients with malignant disease. Evidence of a thrombus in the right ventricle indicates a poor prognosis with a higher rate of death at 3 months from the inciting event. Unfortunately, in our case, the patient died less than 3 months after her initial presentation.

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REFERENCES