A 54-year-old man presented to the emergency department with acute shortness of breath and fatigue for 3 days. He noted increased dyspnea on exertion, such as walking to the mailbox, which progressively worsened to extreme dyspnea at rest, associated with anxiety caused by air hunger. He denied any recent weight change, cough, fever, chills, chest pain, headache, nausea, vomiting, diarrhea, or recent travel outside of the southeastern United States.

The patient had a past medical history of obstructive sleep apnea and obesity hypoventilation syndrome on nightly continuous positive airway pressure (CPAP). In addition, he was diagnosed with pT4b left great toe melanoma status post-left great toe amputation, with recurrence on his left lower extremity. Positron-emission tomography-computed tomography (PET-CT) at relapse revealed a solitary pulmonary nodule suggestive of metastatic disease, for which he was started on nivolumab and ipilimumab, approximately 2 months before admission. On routine laboratory tests after receiving his initial dose of immunotherapy, the patient was noted to have significantly elevated liver function levels. He was diagnosed with asymptomatic hepatitis, thought to be secondary to immunotherapy, for which he completed a prednisone course approximately 2 months before admission. Nivolumab and ipilimumab were discontinued and had not yet been restarted at the time of admission while awaiting resolution of elevated liver enzymes.

In the emergency department, the patient was afebrile, with a heart rate of 86 beats per minute, blood pressure of 143/86 mm Hg, respiratory rate of 35 breaths per minute, with oxygen saturation of 92% on 2 liters of oxygen via nasal cannula. On initial examination, the lungs were clear to auscultation bilaterally without rales, rhonchi, or wheezes. He was tachypneic without accessory muscle use. Cardiac examination revealed no jugular venous distension (JVD), and he had a regular rate and rhythm without murmurs, rubs, or gallops.

Laboratory findings including the following (reference ranges listed parenthetically): hemoglobin, 15.8 g/dL (13.2 to 16.6 g/dL); white blood cell count, 12.5 x 10^9/L (3.4 to 9.6 x 10^9/L); platelet count, 224 x 10^9/L (135 to 317 x 10^9/L); serum urea nitrogen, 18 mg/dL (8 to 24 mg/dL); creatinine, 0.67 mg/dL (0.74 to 1.35 mg/dL); glucose, 153 mg/dL (70 to 140 mg/dL); alanine aminotransferase, 354 U/L (7 to 55 U/L); aspartate aminotransferase, 98 U/L (8 to 48 U/L); total bilirubin, 0.3 mg/dL (<1.2 mg/dL); NT-Pro brain natriuretic peptide, <25 pg/mL (<67 pg/mL); creatine kinase, 660 U/L (39 to 308 U/L). His initial high-sensitivity troponin level of 806 ng/L (<15 ng/L) upon admission increased to 900 ng/L at 2 hours and 1189 ng/L at 6 hours.

Chest x-ray film showed no signs of pulmonary edema, cardiomegaly, or focal consolidations. Electrocardiogram (ECG) demonstrated normal sinus rhythm without ST-segment changes and was unchanged from previous ECGs. Transthoracic echocardiogram (TTE) revealed no pericardial effusion, calcified aortic valve without stenosis or regurgitation, normal mitral valve, normal right ventricular size and function, and normal left ventricular size with mild concentric increase in wall thickness with an estimated left ventricular ejection fraction of 75% to 80%.
1. Which one of the following diagnoses should most likely be ruled out first in this patient?
   a) Acute coronary syndrome (ACS)
   b) Acute pericarditis
   c) Myocarditis
   d) Cardiac tamponade
   e) Pulmonary embolism

   Acute coronary syndrome, which can be subclassified as unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction, is a clinical syndrome classically involving exertional, substernal chest pain, suggestive of myocardial infarction ischemia. Troponin elevation is a nonspecific marker of myocardial damage that can differentiate unstable angina from myocardial infarction in this syndrome; however, our patient had no chest pain, making ACS less likely in this patient.

   Four primary diagnostic criteria are associated with pericarditis, including pleuritic chest pain that improves with sitting forward, ECG changes (PR depression or diffuse ST-elevation), and pericardial friction rub on auscultation and pericardial effusion. Our patient presented with none of these findings, so acute pericarditis was unlikely.

   Myocarditis presents with a nonspecific clinical presentation including dyspnea, chest pain, arrhythmias, or even severe hypotension with cardiogenic shock. Myocarditis is typically a diagnosis of exclusion. Although initial TTE showed normal ejection fraction, this does not rule out myocarditis. Although this patient has several clinical features associated with myocarditis, it is critical to first rule out more common causes of dyspnea, especially as myocarditis requires more sophisticated diagnostic measures.

   Cardiac tamponade classically presents with Beck’s triad of hypotension, JVD, and muffled heart sounds, which were not present in this patient. Furthermore, there was no evidence of effusion or tamponade on echocardiography.

   Malignancy is associated with hypercoagulability. Pulmonary embolism should be strongly considered in a patient with active cancer presenting with tachypnea, hypoxia, and acute dyspnea at rest without consolidations on chest x-ray. Significantly elevated troponin levels can be seen following pulmonary embolism and can be suggestive of right-heart strain.

   Soon after admission, our patient experienced further respiratory decompensation, with increasing dyspnea and oxygen desaturation, requiring escalation to bidirectional positive airway pressure. Because of initial troponin elevation with normal ECG findings and clinical decompensation, there was increasing concern for pulmonary embolism. D-dimer testing was bypassed, and CT angiogram of the chest was obtained, which showed no evidence of pulmonary embolism or coronary thrombus. Lower extremity Doppler ultrasounds were negative for deep vein thrombosis. Troponin T levels continued to rise, peaking at 1394 ng/L at 11 hours following admission.

   Based on the clinical and diagnostic findings above, myocarditis was suspected.

2. Which one of the following tests is most appropriate for diagnosis of myocarditis in this patient?
   a) Cardiac magnetic resonance imaging (MRI)
   b) Myocardial biopsy
   c) Cardiac CT angiography
   d) Coronary catheterization
   e) No further testing is needed

   Cardiac MRI (CMR) has become the diagnostic tool of choice for patients with evidence of acute myocardial injury unrelated to ischemia; CMR can detect multiple features of myocarditis, including inflammatory hyperemia, edema, and necrosis and scarring. When 2 of 3 are present, they fulfill diagnostic criteria for active myocarditis per the 2009 Lake Louise Criteria. Quantitative CMR incorporating native T1 was shown in 2018 to have improved sensitivity for myocarditis compared with the Lake Louise Criteria. Accordingly, use of native T1 alone can simplify the diagnosis of myocarditis. Cardiac MRI also provides
prognostic data for functional and clinical recovery and mortality. The gold standard for definitive diagnosis of myocarditis is an endomyocardial biopsy. Because of its invasiveness and frequent false negative results, a biopsy is not recommended unless there is evidence of left ventricular dilation, which was not present in this patient.

Cardiac CT angiography and coronary catheterization are valuable techniques when evaluating ACS, but they are nonspecific in diagnosing myocardial disease such as myocarditis. Given the low pretest probability of ACS, there was no indication for cardiac CT or catheterization in this patient.

The patient’s dyspnea continued to worsen, with signs and symptoms of heart failure, including profound orthopnea. Because of the patient’s clinical status, CMR was not feasible at that time to confirm the diagnosis of myocarditis radiographically, so the diagnosis was made clinically. Empiric treatment was initiated.

3. Which one of the following is the most likely cause for this patient’s myocarditis?
   a) Viral myocarditis
   b) Medication side effect
   c) Granulomatous inflammatory disease
   d) Giant-cell myocarditis
   e) Lyme myocarditis

   Thorough history and physical examination can often narrow the etiology of myocarditis, although up to 50% of cases remain idiopathic. Viral myocarditis is typically caused by common viruses such as Coxsackievirus B or Parvovirus B19. Recently severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has been implicated in myocarditis. Viral disease is typically accompanied by fever, gastrointestinal, or diarrhea with enteroviruses, arthralgias, rash and hematologic derangements with parvovirus and upper respiratory infection with loss of taste and smell and diarrhea with SARS-CoV-2. No localized or systemic infectious symptoms were present in our patient, making viral myocarditis less likely.

   The most likely etiology of myocarditis in this patient is a medication side effect. Given his recent exposure to dual-agent immunotherapy with nivolumab and ipilimumab, as well as a history of immunotherapy-induced hepatitis, the patient’s clinical presentation of myocarditis within 2 months of drug exposure makes immune checkpoint inhibitor (ICI) myocarditis the most likely diagnosis.

   Patients with chronic dilated cardiomyopathy presenting with myocarditis and new-onset ventricular arrhythmias are more likely to have cardiac sarcoidosis. Giant-cell myocarditis is distinguished from viral myocarditis by the presence of arrhythmias, such as ventricular tachycardia and complete heart block, with rapid onset and progressively worsening clinical course despite optimal therapies. Our patient did not present with arrhythmias or other signs of systemic granulomatous disease, making sarcoidosis and giant-cell myocarditis less likely.

   Myocarditis is a known complication of Lyme disease, often presenting with heart failure and atrioventricular conduction abnormalities in people with recent travel to endemic areas of Lyme disease, primarily the northeastern United States. Our patient did not have conduction delays on ECG and had no recent travel to areas endemic for Lyme disease, making this diagnosis less likely.

4. Which one of the following is the best initial treatment for this patient?
   a) Intravenous immunoglobulin (IVIG)
   b) High-dose corticosteroids
   c) Infliximab
   d) Antithymocyte globulin
   e) Implanted cardiac defibrillator (ICD) placement

   There is currently no strong evidence for the use of IVIG in the treatment of myocarditis, although there are several small studies reporting success, including a case report regarding 3 patients with myocarditis.
published in 2020. Thus, IVIG is not considered a first-line therapy at this time.

For severe immune-related adverse events, as seen in our patient, the American Society of Clinical Oncology (ASCO) guidelines currently recommend starting high-dose steroids (prednisone or methylprednisolone at 1 to 2 mg/kg per day) for at least 6 weeks. Retrospective data demonstrate that patients with ICI myocarditis experienced fewer major adverse cardiovascular events (MACE), such as sudden cardiac death, nonfatal cardiac arrest, life-threatening arrhythmias, and cardiogenic shock, when treated with 2.06 mg/kg steroid therapy compared with 0.84 mg/kg steroid therapy. Furthermore, more aggressive dosing, such as methylprednisolone dosed 1 g daily, can be implemented for patients with severe disease with grade 3 to 4 ICI myocarditis.

In patients without an immediate response to high-dose corticosteroids, the addition of other immunosuppressive drugs, such as antithymocyte globulin, mycophenolate, or infliximab, can be considered but are not considered first-line therapies.

Placement of ICDs is typically not indicated for myocarditis. If treated with high-dose steroids, the risk of major adverse cardiac events is dramatically reduced. If arrhythmias persist following adequate first-line therapy, ICD placement could be considered, but it is not indicated in the acute setting as first-line therapy.

The patient received a 3-day course of intravenous methylprednisolone (1 g per day) with significant clinical improvement. By the time of discharge, troponin T was 478 ng/L (<15 ng/L). He was weaned to 3 liters of oxygen via nasal cannula. He was discharged with a 21-day prednisone taper.

5. Which one of the following is the most appropriate course regarding further cancer treatment in this patient?
   a) Resume nivolumab-ipilimumab at the same dose because ICI myocarditis carries a favorable prognosis for antitumor effect
   b) Resume nivolumab-ipilimumab at a lower dose
   c) Start a new immunotherapy agent
   d) Further immunotherapy is contraindicated
   e) No therapies are effective following failure of immunotherapy in advanced melanoma

There have been no studies to date showing a consistent correlation between the development of ICI myocarditis and the antitumor effect of an immunotherapy agent.

Immune checkpoint inhibitor myocarditis is graded in severity (I-V). Abnormal biomarkers without symptoms qualify as grade I. Moderate-to-severe symptoms requiring hospitalization with any cardiac involvement qualify as grade IV. Grade V implies fatality. All patients with grade II to IV ICI myocarditis are recommended for permanent discontinuation of ICI therapy independent of dose and agent. Accordingly, resuming nivolumab-ipilimumab at a lower dose or starting a new therapy, such as pembrolizumab, would be contraindicated.

Multiple therapies are available for patients with advanced melanoma who are not candidates for immunotherapy or who have failed initial immunotherapy. Adjuvant treatment options include targeted tyrosine-kinase inhibitors (eg, dabrafenib-trametinib) in patients with BRAF V600-activating mutations. Direct injection of extracranial tumors with talimogene laherparepvec (T-VEC), high-dose interleukin-2 therapy, and cytotoxic chemotherapies have also been used successfully in advanced, unresectable melanoma.

Our patient was permanently discontinued from immunotherapy. Two weeks after discharge, he had weaned from supplemental oxygen completely and could walk 100 yards independently. Six months after discharge, a PET-CT scan showed a reduction in the size of the solitary pulmonary nodule and no clinical evidence of persistent dermatologic disease.

DISCUSSION
Immune checkpoint proteins, such as PD-1 and CTLA-4, are pro-apoptotic proteins expressed on T-lymphocytes that interact with ligands on antigen-presenting cells.
(eg, dendritic cells), leading to programmed cell death. Tumor cells commonly downregulate the expression of inhibitory checkpoint proteins, thereby evading T-lymphocyte–induced tumor-cell apoptosis. Inhibitors of immune checkpoint proteins were initially approved in 2014, offering a novel cancer therapy in which the immune system is directed to recognize and target cancer cells.9

Ipilimumab, an anti-CTLA-4 antibody, was the first agent approved for patients with advanced melanoma. More recently, combination therapy with nivolumab, an immunoglobulin (Ig) G4 antibody targeted against PD-1, was approved to treat advanced melanoma. Immune-related adverse events (IRAEs) associated with these therapies were identified with skin, pulmonary, gastrointestinal, hepatic, and endocrine organs most affected.11

Myocarditis is a rare but well-documented IRAE seen in patients treated with immunotherapy, especially dual-agent therapy. Myocarditis may present with wide-ranging symptoms from mild chest pain and dyspnea to cardiogenic shock and death. Myocarditis treatment strategies are etiology dependent. The most common cause of myocarditis is viral infection, such as Coxsackievirus B, Parvovirus B19, and Epstein-Barr virus. Other common causes include giant-cell myocarditis, eosinophilic myocarditis associated with drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, sarcoidosis, and systemic lupus erythematosus.7 Patients who present with dyspnea, chest pain, or new-onset heart failure with recent immunotherapy treatment should be suspected of having ICI myocarditis. In a study of 15 patients with ICI myositis, 5 had concurrent myocarditis, and 6 had respiratory muscle paralysis.12 The concomitant presentation of muscular pathology in multiple organ systems suggests that the pathophysiology of ICI myocarditis likely involves muscle-specific antibodies.

The most extensive study of ICI myocarditis was a retrospective and prospective multicenter registry published in 2016, with data on 35 patients with myocarditis following immunotherapy compared with contemporaneously treated patients who did not develop myocarditis. Timing of symptoms is critical in elucidating whether ICI therapy is the underlying cause of myocarditis. The median time to symptom onset following initial ICI treatment was 34 days, with 81% presenting within 90 days.10 Accordingly, any patient who develops symptoms more than 3 months after exposure to ICI therapy should be investigated for alternative causes of myocarditis.

In this study, 20 of 35 patients were diagnosed via CMR, 11 of 35 patients were diagnosed via cardiac biopsy or autopsy, and 4 of 35 patients were diagnosed clinically without biopsy or CMR. Retrospectively, approximately one-half of patients with ICI myocarditis developed major adverse cardiovascular events. Lower diastolic blood pressure on admission and higher troponin T levels on admission and at discharge were the 2 markers carrying significant negative prognosis. There was a 4-fold increased risk of MACE in patients with admission troponin T levels $\geq 1.5$ ng/mL and increased risk of MACE in patients treated with lower steroid doses (2.06 mg/kg methylprednisolone in non-MACE vs 0.84 mg/kg in MACE groups). Patients treated with high-dose steroids (>1 to 2 mg/kg) have a lower incidence of MACE resulting from ICI myocarditis, consistent with our findings in this case.10 There are alternative treatment options, particularly in patients who fail to respond to steroid therapy, including intravenous immunoglobulin, mycophenolate, infliximab, plasmapheresis, alemtuzumab, antithymocyte globulin, and abatacept. For patients who do not clinically respond to glucocorticoid therapy or who continue to have elevated troponin levels, it is recommended to use 1 or more of these agents in addition to steroids. Conventional medical management is also considered standard, including diuretics and ionotropic support for acute decompensated heart failure, standard antiarrhythmic management for tachyarrhythmias, and pacemaker placement for high-risk bradyarrhythmias.
The innovation of immunotherapy has revolutionized modern cancer therapy and is now being used as a first-line treatment for some cancer subtypes. However, side effects are common, and physicians should have a low threshold for evaluating IRAEs resulting from these new therapeutic agents.

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**REFERENCES**


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