A previously healthy 18-year-old man presented with chest pain that awoke him. The pain was described as constant, grade 2/10, left-sided chest pressure without radiation or correlation with exertion. This was preceded by 1 day of nausea, vomiting, and fever to 102°F. He did not have dyspnea, diaphoresis, palpitations, edema, orthopnea, risk factors for venous thromboembolism, recent travel, acute life stressors, trauma, or known connective tissue disorders. He did not have any chronic medical conditions and was not taking any medications as an outpatient. Initial blood pressure was 130/69 mm Hg; heart rate, 68 beats/min; respirations, 20 breaths/min; and oxygen saturation, 99% (room air). He was afebrile. Heart examination found regular rate and rhythm, normal S1/S2; there were no murmurs, rubs, or extra heart sounds. Jugular venous pressure was normal. There was no chest wall tenderness. Lung sounds were equal and clear bilaterally. Peripheral pulses were strong and equal, and there was no peripheral edema. Complete blood count demonstrated the following (reference ranges provided parenthetically): hemoglobin, 15.4 g/dL (13.2 to 16.6 g/dL); platelets, 239 × 10⁹/L (135 to 317 × 10⁹/L); leukocyte count, 7.5 × 10⁹/L (3.4 to 9.6 × 10⁹/L); and normal differential with the exception of elevated monocytes, 0.96 × 10⁹/L (0.26 to 0.81 × 10⁹/L). Metabolic panel showed sodium, 141 mmol/L (135 to 145 mmol/L); potassium, 4.0 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); and creatinine, 1.02 mg/dL (0.74 to 1.35 mg/dL). Chest radiography was unremarkable. Electrocardiography demonstrated 2- to 3-mm ST-segment elevations in the inferior leads with ST-segment depressions in leads V1 to V3 (Figure 1); troponin T was elevated at 2317 ng/L (normal, <15 ng/L).

1. What is the best next step in management of this patient?
   a. Colchicine
   b. Nonsteroidal anti-inflammatory drugs
   c. Computed tomography angiography of the chest
   d. Coronary angiography
   e. Echocardiography

Colchicine and nonsteroidal anti-inflammatory drugs can be used to reduce inflammation in states such as pericarditis and myocarditis, but it is important to verify these diagnoses and to exclude other diagnoses before treatment. Computed tomography angiography of the chest can be used to diagnose pulmonary embolism, aortic dissection, and stable coronary disease. Coronary angiography is the best option for this patient presenting with a clinical picture consistent with ST-segment elevation myocardial infarction. Echocardiography allows visualization of regional wall motion abnormality but is purely diagnostic, whereas angiography has potential therapeutic value. Our patient was at a non–percutaneous coronary intervention–capable center within 120 minutes of a percutaneous coronary intervention–capable hospital, so he was transferred for emergent angiography. Before transfer, he was given 324 mg of aspirin and 600 mg of clopidogrel, and intravenous administration of unfractionated heparin was initiated. On angiography, he was free of obstructive coronary disease, and there was no evidence of vasospasm or coronary artery dissection. He remained hemodynamically stable on admission with cessation of chest pain. He did have persistent ST elevations in the inferior leads, and troponin trended from 2045 ng/L on arrival to 1994 ng/L at 2 hours to 2070 ng/L at 6 hours. Urine drug screen was negative. Polymerase chain reaction (PCR) was negative for
COVID-19. C-reactive protein level was mildly elevated at 10.4 mg/L (≤8.0 mg/L).

2. What is the most likely diagnosis for this patient?
   a. Takotsubo (stress) cardiomyopathy
   b. Myocardial infarction from vasospasm
   c. Embolic myocardial infarction
   d. Pericarditis
   e. Myocarditis

   Takotsubo cardiomyopathy may explain the elevated troponin but typically is manifested with more diffuse ST-segment and T-wave changes. Vasospasm is certainly in the differential diagnosis, although persistent ST elevations in the absence of chest pain argue against this. Embolism is a possibility, although this patient is young and healthy with very few risk factors for a source of embolization. Pericarditis generally presents with diffuse ST-segment elevations and would not cause the significant troponin elevations seen in our patient. Myocarditis is higher on the differential list and can be manifested with focal ST changes on the basis of which area of myocardium is affected as well as with elevated inflammatory markers as seen in this patient. In our patient with elevated troponin and ST-segment elevations within a single vascular distribution, we proceeded to testing that was focused on distinguishing myocardial infarction from myocardial injury due to a nonvascular cause.

3. What is the next best test to find a diagnosis in this patient?
   a. Provocative acetylcholine testing
   b. Cardiac magnetic resonance imaging (cMRI)
   c. Transthoracic echocardiography
   d. Transesophageal echocardiography
   e. Endomyocardial biopsy

   Acetylcholine administration during angiography would test for vasospasm, but there was low suspicion for this as mentioned before. The negative drug screen further supports this low likelihood. Cardiac MRI is a noninvasive test to differentiate myocardial infarction from myocardial inflammation and is the preferred next test. Transthoracic echocardiography may show regional wall motion abnormality, but it still does not determine the cause of any regional dysfunction. It can be helpful to diagnose stress cardiomyopathy, in which significant wall motion abnormality occurs, classically in the apex. Transesophageal echocardiography is useful to identify a source of embolism, but this was unlikely in our patient. Endomyocardial biopsy can definitively diagnose inflammation or necrosis, but it is an invasive test with potential complications. In addition, the affected tissue may not be sampled if inflammation is patchy. Our patient underwent cMRI, which demonstrated early and late subepicardial gadolinium enhancement in the inferior, inferoseptal, and inferolateral walls from apex to base, involving 50% of

FIGURE 1. Electrocardiogram demonstrating 2- to 3-mm ST-segment elevations in the inferior leads with ST-segment depressions in leads V1 to V3.
the myocardial thickness (Figure 2). These findings confirmed severe inflammation, consistent with myocarditis. Fortunately, there was only mild hypokinesis of the affected segments on MRI with preserved left ventricular ejection fraction of 60%.

4. Which of the following is the most likely culprit for inciting this patient’s myocardial inflammation seen on MRI?
   a. Viral infection
   b. Sarcoidosis
   c. Bacterial infection
   d. Eosinophil infiltration
   e. Giant cell infiltration

   The patient did have a prodromal illness that seemed viral in nature (transient nausea, vomiting, and fever), and viruses remain the most common cause of myocarditis. Whereas sarcoidosis can involve the myocardium, it is unlikely in a young, healthy patient with sudden onset of symptoms. Bacterial infection of the heart typically causes endocarditis rather than myocarditis. He was generally healthy, was not taking any medications, and had no eosinophilia, making eosinophilic (hypersensitivity) myocarditis less likely. Last, giant cell myocarditis is possible, but this is usually manifested with fulminant myocarditis and acute heart failure. The patient was retested for COVID-19, given high suspicion, and a routine respiratory pathogen panel was obtained. Results of both tests were negative. The cause was presumed to be viral on the basis of the clinical history. He was managed conservatively while in the hospital and was ultimately started on colchicine 0.6 mg twice daily to be continued for a month, given the severity of inflammation on MRI.

5. Which one of the following tests should be ordered in the outpatient setting for prognostic value?
   a. C-reactive protein
   b. Endomyocardial biopsy
   c. Electrocardiography
   d. Echocardiography
   e. cMRI

   C-reactive protein would reveal active inflammation but is not specific to myocarditis and does not provide prognostic value. Endomyocardial biopsy is indicated only if it would change treatment or if there is persistent heart failure or dilated cardiomyopathy with unclear etiology. Electrocardiography may or may not have continued changes, although it would not provide prognostic value. Echocardiography would provide information about regional wall motion and ejection fraction. However, our patient had normal ejection fraction with minimal wall motion abnormality to begin with, and echocardiography does not provide as detailed imaging of myocardial inflammation as cMRI does. Repeated cMRI would provide prognostic value because it permits visualization of the progression of disease over time. The patient was dismissed with cMRI in 6 months.

DISCUSSION
Myocarditis—inflammation of the myocardium—can be caused by a variety of infectious organisms (viruses, parasites) or autoimmune conditions (eosinophils, giant cellitis, sarcoidosis). The patient had a prodromal illness that seemed viral in nature, and viruses remain the most common cause of myocarditis. Bacterial infection of the heart typically causes endocarditis rather than myocarditis. The patient was managed conservatively while in the hospital and was ultimately started on colchicine 0.6 mg twice daily to be continued for a month, given the severity of inflammation on MRI. Repeated cMRI would provide prognostic value because it permits visualization of the progression of disease over time. The patient was dismissed with cMRI in 6 months.
cells, lupus, sarcoidosis). Our patient had presumed viral myocarditis. In viral myocarditis, there is virus-mediated injury followed by recruitment of lymphocytes to the area of injury, which is mediated by cytokines. Subsequently, there is further myocardial injury, edema, and some degree of autoantibody production as antigens are exposed. There is ongoing investigation into the exact pathophysiologic mechanism by which COVID-19 myocarditis occurs. Current theories include direct injury through an angiotensin-converting enzyme 2–mediated mechanism, cytokine dysregulation, and autoimmune response to viral injury.

This inflammation can be manifested in a variety of ways, some of which mimic other cardiovascular conditions. This may make the diagnosis more challenging. Myocarditis can mimic acute coronary syndrome with regional ST-segment or T-wave changes, elevated troponin, and regional wall motion abnormalities on echocardiography. Another common presentation is acute or progressive decompened heart failure with or without dilated cardiomyopathy. Last, it can present as sudden cardiac death, life-threatening arrhythmias, or cardiogenic shock. It is important to rule out other life-threatening conditions in the differential diagnosis. In our patient, ruling out acute coronary syndrome with coronary angiography was the proper first step in investigation because of the electrocardiographic changes suggestive of ongoing myocardial injury.

The “gold standard” for diagnosis of myocarditis is endomyocardial biopsy (EMB) with histologic (Dallas criteria) or immunohistologic analysis with viral PCR. However, this is an invasive test with serious possible complications, such as free wall rupture and tamponade. Furthermore, sensitivity of EMB is limited. One reason for this is that inflammation may be patchy, so obtaining an affected sample is left to chance. Furthermore, inflammation is generally subepicardial; thus, biopsy of the endomyocardium reduces the chances of yielding affected tissue. Major societies advocate for the use of EMB only if diagnosis is uncertain or EMB results would change treatment.

A less invasive and increasingly common way to diagnose myocarditis is cMRI. In one study, cMRI had a sensitivity of 81%, a specificity of 71%, and an accuracy of 79% in patients with viral myocarditis compared with the gold standard of EMB. Characteristic features include subepicardial early and late gadolinium enhancement on T2-weighted images. The specific criteria for diagnosis were formulated by experts and are known as the Lake Louise criteria. We decided to take this less invasive approach in our patient to minimize risk while narrowing our differential diagnosis to guide treatment. We also ordered follow-up cMRI 6 months later for prognostic purposes. One study of 187 patients with myocarditis who were observed for a median duration of 7 years found a statistically significant increase in mortality in patients with persistent late gadolinium enhancement without edema at 6 months. The main predictor of mortality in myocarditis is biventricular dysfunction; young age, long-lasting symptoms, giant cell etiology, heart failure symptoms, low left ventricular ejection fraction on presentation, and viral PCR positivity are other poor prognostic factors.

Therapy for myocarditis is aimed at reduction of myocardial inflammation and treatment of symptoms. Any complications of myocarditis, such as heart failure or arrhythmias, should undergo the usual guideline-directed therapies. If an inflammatory or autoimmune disorder is responsible for the inflammation, immunosuppression is indicated. In viral myocarditis, supportive care is generally indicated while the body takes care of the inflammation. It was previously thought that corticosteroids may help reduce inflammation in viral myocarditis, especially considering that there is likely to be some degree of autoantibody production after the initial insult. However, a randomized controlled trial in 1995 reported no benefit in
ejection fraction improvement for patients with myocarditis randomized to usual care vs immunosuppressive therapy with either prednisone or azathioprine. In addition, a meta-analysis of 8 randomized controlled trials demonstrated no statistically significant mortality benefit to use of corticosteroids in viral myocarditis. Treatment of COVID-19 myocarditis remains elusive as there is insufficient data to support any one treatment. However, colchicine, corticosteroids, intravenous immune globulin, and cytokine-specific therapies are under investigation.

Colchicine is an agent that is well established for treatment of pericarditis but only experimental in myocarditis. It works through inhibition of neutrophil chemotaxis, NLRP3 inflammasome activity, and interleukin 1 production, thereby decreasing inflammation. For myocarditis, colchicine is promising in the limited evidence supporting its use. In one study of patients with viral myocarditis, 63% of patients receiving colchicine had complete resolution of inflammation on follow-up cMRI vs only 38% of patients who did not receive colchicine. We elected to prescribe our patient colchicine on the basis of these data and the severe inflammation seen on cMRI. Last, major societies recommend exercise restriction while inflammation is present, although this is based on expert opinion and is not formally studied in humans.

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Correspondence: Address to Rekha Mankad, MD, Department of Cardiovascular Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (Mankad.rekha@mayo.edu).

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