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A young man with acute chest pain

A young man presents with severe, pressure-like, midsternal, nonradiating pain, rated 10 on a scale of 10

An 18-year-old man without any significant medical history was transferred from another hospital for higher-level care after presenting with unremitting chest pain. He had been in his usual state of good health until 7 days before presentation, when he developed mild rhinorrhea and a sore throat, but not a cough. He went to an outpatient clinic, where a rapid test for group A streptococci was done; the result was negative, and he was sent home on supportive measures.

On the day of admission, he awoke with severe, pressure-like, midsternal, nonradiating pain, which he rated 10 on a scale of 10. The pain intensified in the supine position and improved with sitting. A complete review of systems was otherwise negative. He denied having had similar symptoms in the past, as well as sick contacts, recent travel, toxin exposure, illicit substance abuse, pets at home, or tick bites. His family history was negative for cardiac arrhythmias, premature coronary artery disease, thoracic aneurysms or dissection, and infiltrative disorders. His surgical and social histories were unremarkable. He said he had no drug allergies.

An electrocardiogram was obtained (**Figure 1**). His troponin I level was 7.0 ng/mL (reference range < 0.04 ng/mL).

On examination, his temperature was 38.1°C (100.6°F), heart rate 101 beats per minute, blood pressure 142/78 mm Hg, respiratory rate 16 breaths per minute, and oxygen saturation 98% on room air. He appeared anxious but was in no acute distress. Neck examination showed no elevation in jugular venous pulsation, bruits, thyromegaly, or lymphadenopathy. Cardiac examination revealed tachycardia without murmurs, rubs, or gallops. Lungs were clear to auscultation. Examination of all 4 extremities found 2+ pulses (on a scale of 0 to 4+) throughout and no cyanosis, clubbing, or edema. Abdominal, neurologic, and dermatologic examinations were unremarkable.

Further blood testing revealed the following:

- Troponin I (3 hours after the first level) 15.5 ng/mL
- B-type natriuretic peptide 200 mg/dL (reference range 0–100 mg/dL)
- C-reactive protein 0.9 mg/dL (reference range 0.0–0.8 mg/dL)
- Erythrocyte sedimentation rate 10 mm/h (reference range < 15 mm/h).

Metabolic and hematologic assessments were unremarkable. A toxicology screen for drugs of abuse was negative. Viral serologic testing was not done.

A chest radiograph showed no acute cardiopulmonary processes.

Given his presenting symptoms, persistent tachycardia, rapidly rising troponin I level, and electrocardiogram showing diffuse ST elevation, he was taken for urgent cardiac catheterization. Coronary angiography revealed no evidence of atherosclerotic disease, acute thrombosis, dissection, or aneurysm. Echocardiography 2 hours after the procedure showed a normal ejection fraction and no regional wall-motion abnormalities or valvular heart disease.

FURTHER TESTING

1 Which test should be done next to further evaluate this patient's chest pain?

- ☐ Serum viral serologic testing
- ☐ Serum free light chain assay
- ☐ Nuclear myocardial perfusion study
- ☐ Cardiac magnetic resonance imaging (MRI)
- ☐ Endomyocardial biopsy

In this patient without ischemic coronary disease or valvular heart disease, the recent upper

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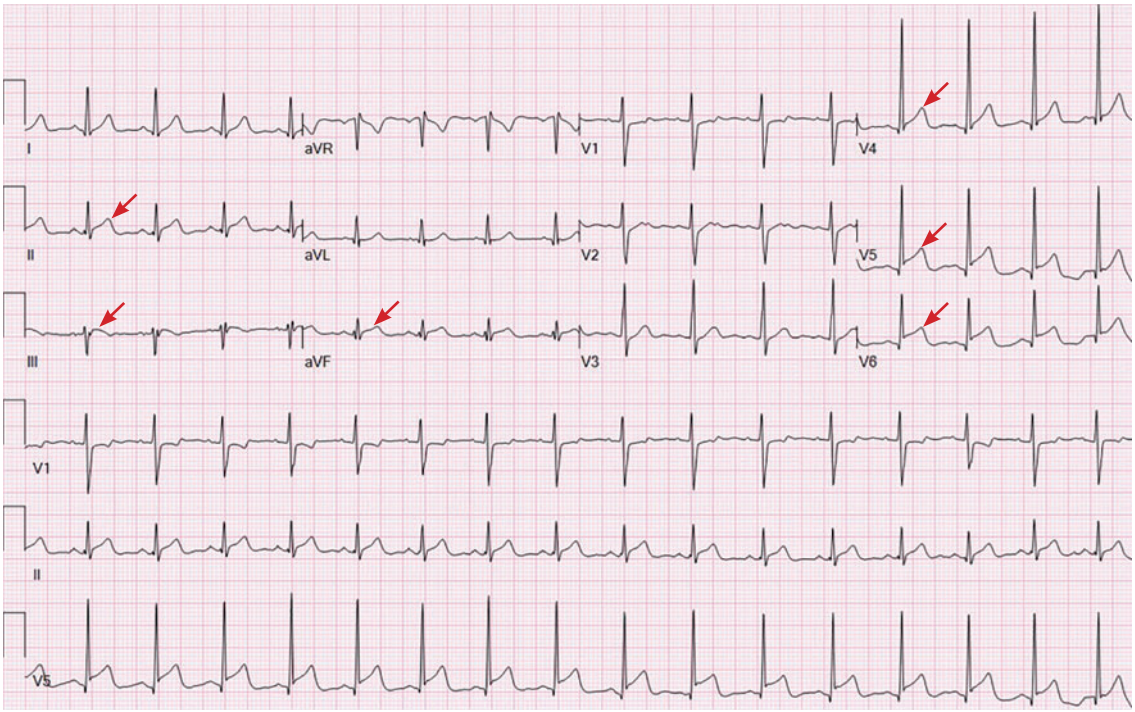

Figure 1. The patient's electrocardiogram on presentation shows ST-segment elevation (arrows) over the lateral and inferior distribution (V_4–V_6, II, III, and aVF).

respiratory tract prodrome, active positional chest pain, and diffuse electrocardiographic changes raise the possibility of myocarditis with pericardial involvement.

Viral serologic tests

Viral serologic tests are often obtained in the workup of myocarditis as a noninvasive means of detecting an infectious cause.

However, this approach has several problems. First, a positive serologic result is a signal of the peripheral immune response to a pathogen but does not necessarily indicate active myocardial inflammation. Additionally, circulating immunoglobulin G against cardiotropic viruses is commonly found, even in the absence of myocarditis.[1] This is often the result of a high prevalence and exposure to these viruses in the general population. Further, trials have shown no correlation between serologic results and organisms identified by endomyocardial biopsy.[2]

Thus, serologic testing seems to be of limited utility, reserved for testing for infection with *Borrelia burgdorferi* (Lyme disease) in endemic areas, hepatitis C virus, human immunodeficiency virus in patients at high risk, *Rickettsia conorii*, and *Rickettsia rickettsii*.[3]

Serum free light chain testing for amyloidosis

Serum free light chain testing is replacing serum and urine protein electrophoresis in the workup of cardiac amyloidosis,[4] as electrophoresis has poor sensitivity.[4,5]

Cardiac amyloidosis often affects older persons, although in rare cases it can affect young patients who carry mutations in the transthyretin gene (ATTR amyloidosis).[6] This diagnosis is unlikely in our patient, as he has no other affected organ systems (amyloidosis often affects the renal and neurologic systems), normal QRS voltages on electrocardiography (which are often but not always low in amyloidosis), and no left ventricular hypertrophy or diastolic dysfunction on echocardiography (which are often seen in amyloidosis).[4]

Nuclear perfusion imaging for sarcoidosis

Nuclear imaging has a limited role in evaluating myocarditis,[3] but positron-emission tomography with fluorine-18 fluorodeoxyglucose has a diagnostic role in sarcoidosis, an immune-mediated cause of myocarditis.[7]

His troponin I level had risen from 7.0 to 15.5 ng/mL in 3 hours

Based on the acuity of the patient's presentation, preceded by upper respiratory tract symptoms, sarcoidosis is less likely. Sarcoidosis is difficult to diagnose, although when it is the cause of myocarditis, some clues exist, as patients usually present with heart failure symptoms, a second- or third-degree atrioventricular block, or a dilated left ventricle on echocardiography.[3] All of these were absent in our patient.

Cardiac MRI

Cardiac MRI has undergone many advances, making it an extremely useful noninvasive test. It has excellent utility as a stand-alone test in diagnosing myocarditis and has synergistic value when combined with endomyocardial biopsy.[8] It is indicated in hemodynamically stable patients with a clinical suspicion of myocarditis, persistent symptoms, absence of heart failure, and when imaging findings will change management. It is particularly useful to help elucidate a cause and guide tailored therapy.[9] Therefore, it is a reasonable next step in the diagnostic pathway for this patient.[10]

Cardiac MRI also allows for concurrent assessment of scar. In myocardial infarction, the late gadolinium enhancement is subendocardial or transmural. In myocarditis, the pattern differs, being found in the subepicardial lateral free wall (in most patients with parvovirus B19) and mid-myocardial septum (in most patients with herpesvirus 6).[9,11] Cardiac MRI also confers prognostic information for patients with suspected myocarditis.[12]

His prodrome, positional chest pain, and diffuse ECG changes raise the possibility of myocarditis with pericardial involvement

The Lake Louise criteria[9] for the diagnosis of myocarditis require 2 of the following:

- Evidence of myocardial edema
- Increased ratio of early gadolinium enhancement between myocardium and skeletal muscle (indicates hyperemia)
- At least 1 focal lesion with nonischemic late gadolinium enhancement (indicates cardiac myocyte injury or scarring).

The Lake Louise criteria may be replaced by T1 and T2 mapping, which was found to be considerably better for diagnosing myocarditis when the 2 were compared.[9,13,14]

Endomyocardial biopsy

Endomyocardial biopsy should not be delayed while waiting for cardiac MRI in patients who are hemodynamically unstable or present with life-threatening features (ventricular arrhythmia, left ventricular failure, or resuscitation after sudden cardiac death).[3,10]

The indications for endomyocardial biopsy have been highly debated. The 2013 guidelines from the European Society of Cardiology (ESC) recommending endomyocardial biopsy in all clinically suspected cases of myocarditis have only heightened the controversy.[3] The American Heart Association (AHA) guidelines reserve biopsy for patients with suspected myocarditis who have acute or subacute heart failure symptoms or who do not respond to standard medical therapy.[15] Other reasonable indications may include the following: myocarditis with life-threatening ventricular arrhythmias, suspicion of giant cell myocarditis, necrotizing eosinophilic myocarditis, or cardiac sarcoidosis.[16]

Endomyocardial biopsy is the only way to make a definitive diagnosis of myocarditis.[3] However, given the patchy distribution of myocardial involvement, a negative result does not rule out myocarditis. The diagnostic utility can be improved by increasing the number of samples taken (at least 3 but up to 10), obtaining samples from both ventricles, and using cardiac MRI data to determine which sites to biopsy.[3,13,17,18]

Noninvasive testing such as cardiac MRI does not distinguish cell type or etiology (viral vs nonviral).[3] Further, endomyocardial biopsy must be performed before immunosuppressive therapy can be safely started.[3,16] At experienced centers, the complication rate is 0% to 0.8%.[3] The addition of immunohistochemical testing and viral genomic detection by polymerase chain reaction testing have increased the sensitivity of this technique.[19] Finally, endomyocardial biopsy can help rule out some of the other possibilities in the differential diagnosis for myocarditis, including infiltrative and storage diseases, and possibly cardiac tumors.[3]

Of additional note, the diffuse ST-segment elevation seen on the patient's electrocardiogram (**Figure 1**) is indicative of subepicardial inflammation. Since the distribution involves more than one epicardial coronary territory, this helps to differentiate the changes from those that occur with myocardial infarction.[20]

CASE CONTINUED

The patient underwent cardiac MRI, which showed myocardial edema and patchy areas of late gadolinium enhancement, raising suspicion for myocarditis (**Figure 2**).

Causes of myocarditis are numerous (**Table 1**),[3,21,22] but viral and postinfectious etiologies remain the most common causes of acute myocarditis.[23]

2 What is the most likely causative infectious agent?

- ☐ Parvovirus B19
- ☐ Coxsackievirus B
- ☐ Adenovirus species
- ☐ Human herpesvirus 6
- ☐ *Staphylococcus aureus*
- ☐ *Corynebacterium diphtheria*
- ☐ *Trypanosoma cruzi*
- ☐ Influenza H1/N1

INFECTIOUS CAUSES OF MYOCARDITIS

Coxsackievirus B was the agent most often linked to this condition from the 1950s through the 1990s. However, in the last 2 decades, adenovirus species and human herpesvirus 6 have been increasingly encountered, and recently, parvovirus B19 has been credited as the most common culprit,[11,23] at least in the Western world. In developing nations, *T cruzi* and C *diphtheria* are the most common offenders.[21]

S aureus is a common cause of endocarditis, but it rarely plays a role in myocarditis. When it does, the myocarditis is often the sequela of profound bacteremia. This was much more common before antibiotics were invented.[24,25]

Influenza H1/N1 is not among the most common causes of viral myocarditis, but it should be considered during flu season, given its ability to result in fulminant myocarditis.[3,26]

TREATMENT FOR MYOCARDITIS

3 Which treatment is the most appropriate at this time?

- ☐ Intravenous immunoglobulin
- ☐ Interferon beta
- ☐ Acyclovir
- ☐ Prednisone
- ☐ Colchicine

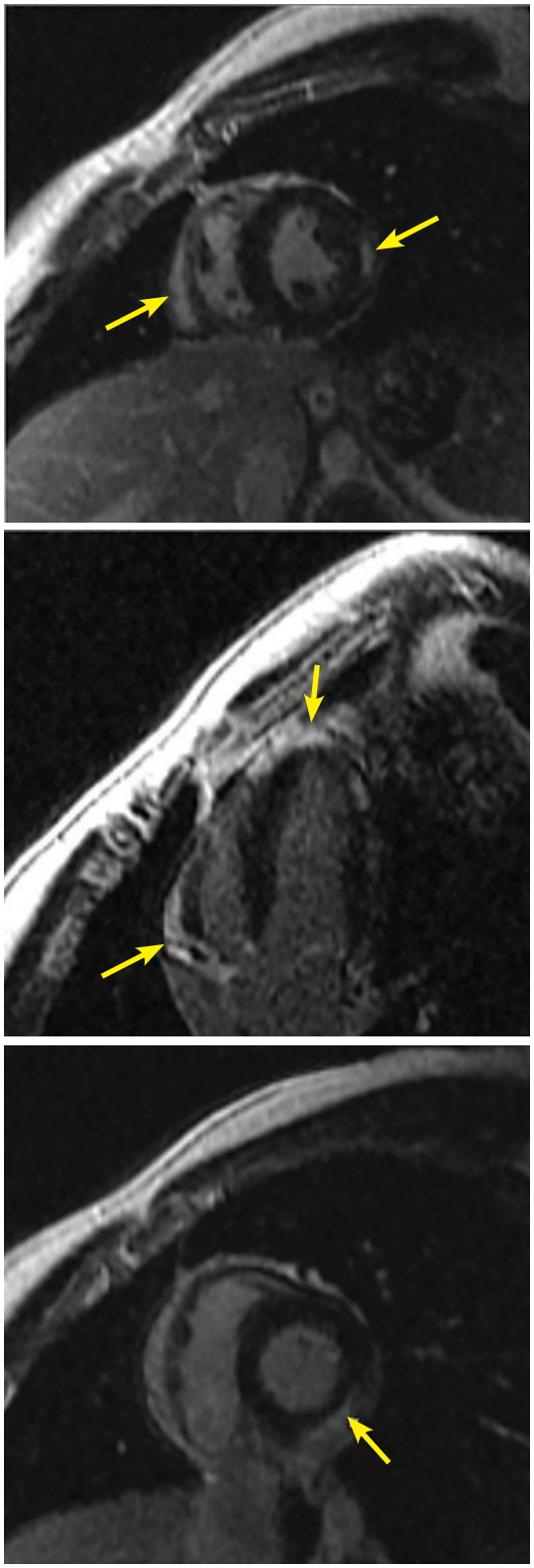

Figure 2. Cardiac magnetic resonance imaging shows areas of patchy subepicardial late gadolinium enhancement (arrows).

Cardiac MRI showed myocardial edema and patchy areas of late gadolinium enhancement

TABLE 1

Selected causes of myocarditis

INFECTIOUS

Viral
Parvovirus B19
Coxsackie B (enterovirus)
Adenovirus
Human herpesviruses
Cytomegalovirus
Epstein-Barr virus,
Human herpes virus 6
Human immunodeficiency virus
Influenza A/B
Poliovirus
Hepatitis C

Bacterial
Borrelia
Rickettsia
Coxiella
Staphylococcus
Streptococcus
Corynebacterium diphtheria
Mycobacterium

Protozoal
Trypanosoma cruzi
Toxoplasma
Babesia

Parasitic
Trichinella spiralis
Taenia solium

Fungal
Aspergillus
Candida
Histoplasma
Mucormycosis
Sporothirix

IMMUNE-MEDIATED

Allergens
Tetanus toxoid
Vaccines (especially smallpox)
Serum sickness

Autoantigens
Infection-negative giant cell
Systemic lupus erythematosus
Rheumatoid arthritis
Sarcoidosis

Alloantigens
Heart transplant rejection

TOXIC

Drugs
Amphetamines
Cocaine
Lithium
Clozapine
Anthracyclines (doxorubicin)
Mesalamine
Sulfonamides (hypersensitivity)
Penicillins (hypersensitivity)
Immune checkpoint inhibitors
(ipilimumab, pembrolizumab, nivolumab)

Heavy metals
Iron
Copper
Lead (rare)

Physical agents
Radiation

Hormones
Pheochromocytoma (epinephrine, norepinephrine)

Miscellaneous
Insect bites
Scorpion sting
Inhalants
Arsenic

Based on information in references 3, 21, and 22.

***S aureus* is a common cause of endocarditis, but it rarely plays a role in myocarditis**

Treatment for myocarditis depends on the cause but always includes supportive care to address the constellation of presenting symptoms. Standard therapies for tachy- or brady-arrhythmias, heart failure, and hemodynamic derangement should be started.

Supportive care

In patients with severe left ventricular dysfunction, an implantable cardiac electronic device, left ventricular assist device, or heart transplant may ultimately be needed. However, if possible these should be deferred for

several months to determine response to treatment, since the myocardium can possibly recover.[16]

Diuretics, beta-blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and aldosterone antagonists should be given as part of guideline-directed medical therapy for patients with heart failure and reduced ejection fraction.[3,27] However, whether and how the patient should be weaned from these agents after disease recovery are unknown.[3]

Intravenous immunoglobulin

Intravenous immunoglobulin in high doses has had mixed results. Its efficacy is well documented in children,[21] but limited supportive data are available in adults.[3] As such, recent ESC guidelines do not provide recommendations regarding its use in adults.[3]

Interferon beta

Interferon beta has shown promise in improving New York Heart Association class and left ventricular ejection fraction.[3] This is attributed to its effects on eliminating adenoviral species and enteroviruses. Treatment of enteroviral organisms in particular has been associated with improved 10-year prognosis.[3] Interferon beta also has in vitro data showing efficacy at diminishing apoptosis from parvovirus B19.[28]

Nucleoside analogues

Empiric treatment with nucleoside analogues (acyclovir, ganciclovir, and valacyclovir) has been tried for patients in whom human herpesvirus is suspected as the causative organism, although with unconfirmed effects.[3] Consultation with an infectious disease specialist is recommended before starting these agents, and biopsy is often needed beforehand.[3]

Immunosuppressive agents

Immunosuppressive agents such as prednisone, azathioprine, and cyclosporine can be used in cases of biopsy-proven disease with manifestations of severe heart failure, especially if biopsy results reveal sarcoidosis, giant cell myocarditis, or necrotizing eosinophilic myocarditis. Although the results were neutral in the Myocarditis Treatment Trial,[29] the cause of myocarditis in this trial was unknown. Therapy with such agents should be initiated after active infection is ruled out, which also would require a biopsy.

Colchicine

Mechanisms of chest pain in myocarditis include associated pericarditis and coronary artery vasospasm.[3,23] Our patient's chest pain changed when he changed position, possibly indicating associated pericarditis. In myocarditis with accompanying pericarditis symptoms, colchicine (1–2 mg as an initial dose and then 0.6 mg daily for up to 3 months) can be helpful in alleviating symptoms.[21,30] Thus, starting this agent in a patient who presents with myocarditis in absence of heart failure, arrhythmias, or left ventricular dysfunction is prudent.

Colchicine is used mainly to address the pain associated with pericarditis. For patients who present with pericarditis without myocarditis, nonsteroidal anti-inflammatory drugs (NSAIDs) remain the first-line treatment, with the addition of colchicine leading to faster symptom resolution.[30] The benefit of colchicine for isolated myocarditis is not well established, with only limited data showing some clinical effects.[31]

CASE CONTINUED

The patient was given colchicine 1.2 mg on the first day and then 0.6 mg daily. Within 2 days, his chest pain had resolved. He did not receive any immunosuppressive agents.

Within 2 days of starting treatment, his chest pain had resolved

DISCHARGE INSTRUCTIONS

4 Before discharge, this patient should be instructed to do which of the following?

- ☐ Take over-the-counter NSAIDs to supplement the effects of colchicine
- ☐ Avoid competitive sports and athletics for at least 6 months
- ☐ Call to schedule repeat cardiac MRI
- ☐ No further instruction is needed

NSAIDs are used by themselves or in combination with colchicine in the treatment of pericarditis, but their use may be associated with worse outcomes in myocarditis.[3,21] Thus, their use is not recommended in most cases.[3]

Excessive physical activity should be avoided for at least 6 months after the clinical syndrome resolves. This recommendation

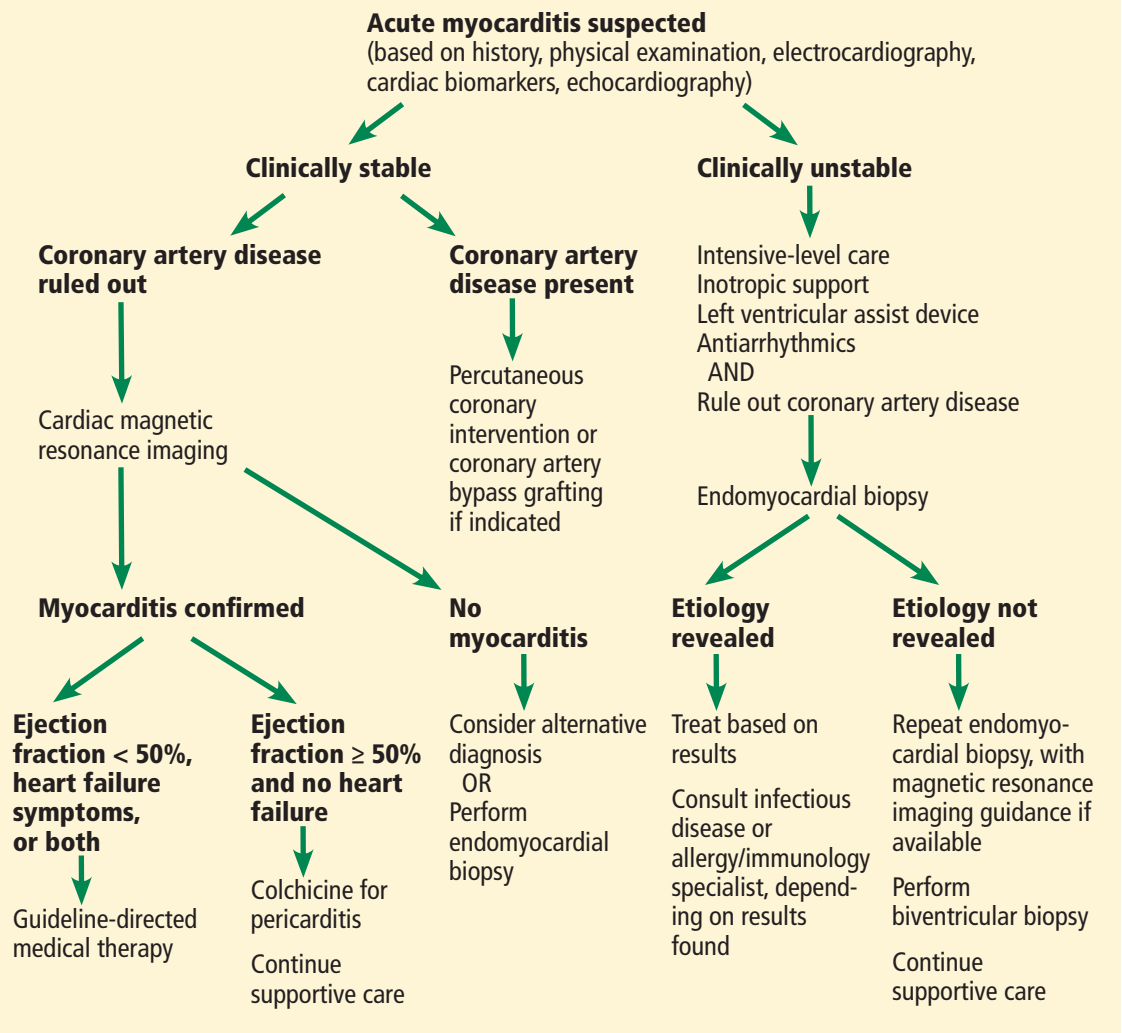

Figure 3. Our suggested approach to suspected acute myocarditis.

At 2 years, he had returned to playing basketball and soccer

is included in the most recent ESC guidelines but is based mainly on expert opinion and murine models with coxsackievirus B.[3] Periodic reassessment is indicated with exercise stress testing before return to strenuous activity.[3,16,32] Testing should look for exercise tolerance, and exercise electrocardiography also helps to evaluate for clinically relevant arrythmias.

Cardiac MRI can help clarify the prognosis in myocarditis, but the role of repeat testing in guiding therapy is limited.[3] Indications for repeat cardiac MRI include presence of 0 or 1 of the Lake Louise criteria (recall that 2 are necessary to make the diagnosis) with recurrence of symptoms and a high suspicion for myocardial inflammation.[3,9] Repeat cardiac MRI was not performed for our patient.

CASE CONCLUDED

The patient was evaluated in the cardiology clinic within 1 week of discharge. At that time, he was in sinus tachycardia with a heart rate of 102 bpm, and he was instructed to avoid any exercise until further notice.

At 6-month follow-up, the sinus tachycardia had resolved. However, because persistent tachycardia had been noted at the first post-discharge visit, and in view of the extent of myocardial involvement, he underwent exercise treadmill testing to evaluate for ventricular arrhythmias. The study did show premature ventricular complexes and 1 ventricular couplet at submaximal exercise levels. As this indicated a higher risk of exercise-induced arrhythmias, he was asked to continue normal

activity levels but to abstain from exercise until the next evaluation.

During his 1-year follow-up, a repeat treadmill test showed no ventricular ectopy. Holter monitoring was ordered and showed no premature ventricular complexes, supraventricular arrhythmias, or atrioventricular block within the 48-hour period.

At his 2-year evaluation, he had returned to playing basketball and soccer on weekends and reported no recurrence of his initial symptoms.

KEY POINTS

- Cardiac MRI has emerged as an excellent noninvasive imaging modality for the diagnosis of myocarditis.
- Treatment of myocarditis depends on the cause and severity of the patient's presentation, spanning the spectrum from conservative care to immunosuppressive agents and even heart failure therapy.
- Excessive physical activity should be avoided for the first 6 months after disease diagnosis and treatment.
- If myocarditis is associated with pericardial involvement, colchicine is the agent of choice, and NSAIDs should be avoided.

Our suggested strategy for approaching myocarditis is shown in **Figure 3**.

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