CLINICAL PROBLEM-SOLVING

A "Hot" Cardiomyopathy

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

A 27-year-old woman presented to the emergency department with sudden onset of palpitations, dyspnea, and chest tightness after smoking cannabis. She also had an episode of vomiting but had no flulike symptoms or other symptoms of infection. She had no known medical conditions and no family history of cardiovascular disease, venous thromboembolism, or sudden cardiac death. She smoked 10 cigarettes a day and occasional cannabis but used no other illicit drugs. She took no regular medications, had not had any recent vaccinations, and had never received vaccination for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For 8 days before admission, she had been taking an unlicensed diet pill containing *Garcinia gummi-gutta* (also known as *Garcinia cambogia*), starch, aloe seeds, cassia seeds, and lotus leaf and had been performing physical exercise, mainly weight lifting.

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The patient's presentation with palpitations, dyspnea, and chest tightness increases suspicion for a tachyarrhythmia. The patient's use of cannabis or the dietary supplement may have been a trigger for the symptoms. *G. cambogia* is a tropical fruit and a popular weight-loss supplement that the Food and Drug Administration considers to be unsafe owing to a risk of toxic effects in the liver. Myocarditis, pulmonary embolism, and acute coronary syndrome should also be considered as a cause of her symptoms, although her young age makes the latter unlikely.

The patient's body temperature was 37°C, heart rate 80 beats per minute, respiratory rate 16 breaths per minute, blood pressure 115/80 mm Hg, and oxygen saturation 98% while she was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 30.2. Cardiovascular examination revealed a regular heart rate with no murmurs. The jugular venous pressure was not elevated, and the lungs were clear on auscultation. Neurologic examination was normal with normal tone, no tremors, and no evidence of limb weakness to suggest a skeletal myopathy. The 12-lead electrocardiogram (ECG) at presentation revealed inferolateral ST-segment elevation. The white-cell count was 8.8×10^9 per liter, with a neutrophil count of 6.2×10^9 per liter (normal range, 1.5 to 6.1), a lymphocyte count of 1.9×10^9 per liter (normal range, 0.8 to 3.5), and an eosinophil count of 0.02×10^9 per liter (normal range, 0 to 0.4). The hemoglobin level was 128 g per liter, and the platelet count was 319×10^9 per liter. Levels of creatinine, calcium, total protein, aminotransferases, albumin, alkaline phosphatase, and C-reactive protein were normal, as were the erythrocyte sedimentation rate and lipid profile.

The creatine kinase level was 4461 IU per liter (normal value, <150), and the troponin T level was 5934 ng per liter (normal value, <14). A polymerase-chain-reaction (PCR) assay for SARS-CoV-2 was negative.

The physical examination is unremarkable; however, the ECG and cardiac biomarkers are abnormal. The most common cause of ST-segment elevation is acute myocardial infarction. Myocardial infarction from rupture of atherosclerotic coronary plaque is very unlikely in a young woman, especially in the absence of a family history of early coronary disease, but spontaneous coronary-artery dissection or coronary-artery spasm should be considered. Acute myocarditis also remains in the differential diagnosis.

The patient was transferred to the catheter suite of the referring tertiary hospital for an invasive coronary angiogram, which revealed smooth unobstructed coronary arteries. Both a bedside echocardiogram before angiography and a formal transthoracic echocardiogram performed in the coronary care unit showed a normal-size left ventricle with globally moderately impaired systolic function and an ejection fraction of 40%. The image quality was limited by body habitus but was suggestive of global hypokinesia, more pronounced at the mid-to-apical segments. A subsequent ECG showed sinus rhythm at 80 beats per minute with a normal QRS duration, no Q waves, and more diffuse ST-segment elevation in the inferior and anterolateral leads (Fig. 1).

The normal coronary angiogram in this young female patient is not surprising. Cardiovascular magnetic resonance imaging (MRI) should be performed to determine whether this event was a myocardial infarction with nonobstructive coronary arteries or was due to a nonischemic process (e.g., myocarditis, takotsubo syndrome, sarcoidosis, or a nonischemic cardiomyopathy).

After returning to her hospital room, the patient was noted to have hypotension (systolic blood pressure, 80 to 90 mm Hg) and runs of nonsustained ventricular tachycardia on cardiac monitoring. She continued to report intermittent chest pain that was mild as compared with the initial episode. Cardiovascular MRI was performed at 1.5 tesla. Extracardiac anatomical examination revealed no pathologic axillary or mediastinal lymph nodes or lung parenchymal abnormalities. The left ventricle was normal in size. The ejection fraction was

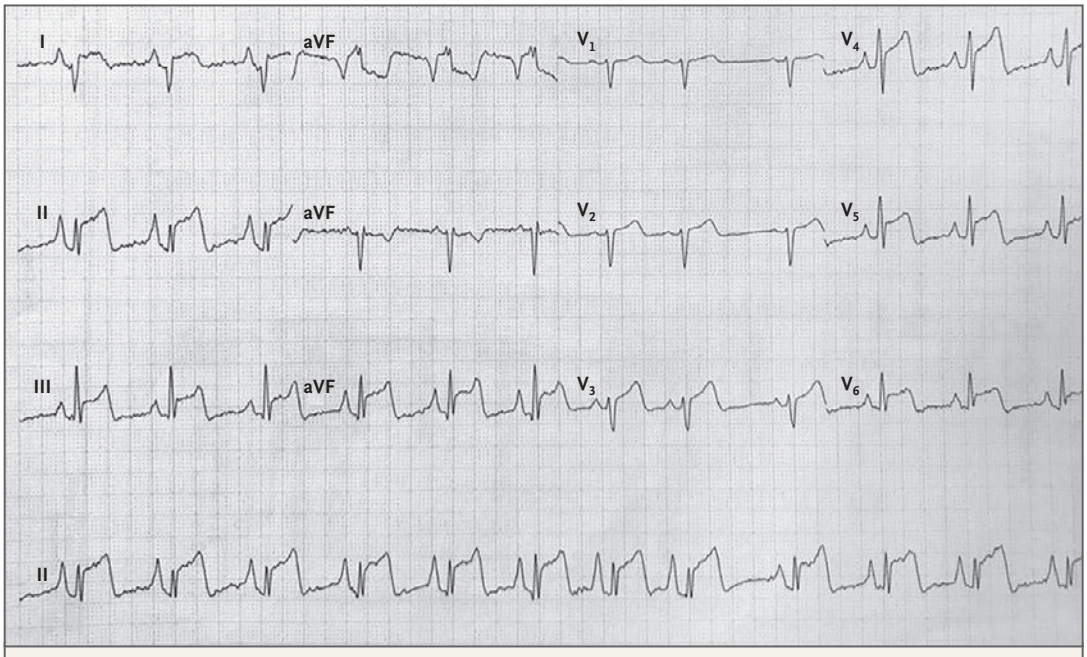

Figure 1. Twelve-Lead Electrocardiogram.
A 12-lead electrocardiogram shows sinus rhythm at 80 beats per minute with normal QRS duration, no Q waves, and ST-segment elevation in the inferior and anterolateral leads.

37% (normal range, 57 to 77); hypokinesis was noted in the inferior, lateral, and septal segments. The right ventricle was normal in size with globally mildly impaired function but no focal changes or aneurysms. Precontrast tissue characterization with mapping acquisitions showed diffusely patchy clinically significant elevation in myocardial T1 (1218 to 1334 msec; normal range, 950 to 1100) and T2 (67 to 75 msec; normal range, 42 to 48) (Fig. 2A). Late post–gadolinium-contrast acquisitions showed strikingly dense circumferential left ventricular epicardial and midwall late enhancement that was transmural in places, with involvement of the right ventricular septum (Fig. 2B and 2C and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

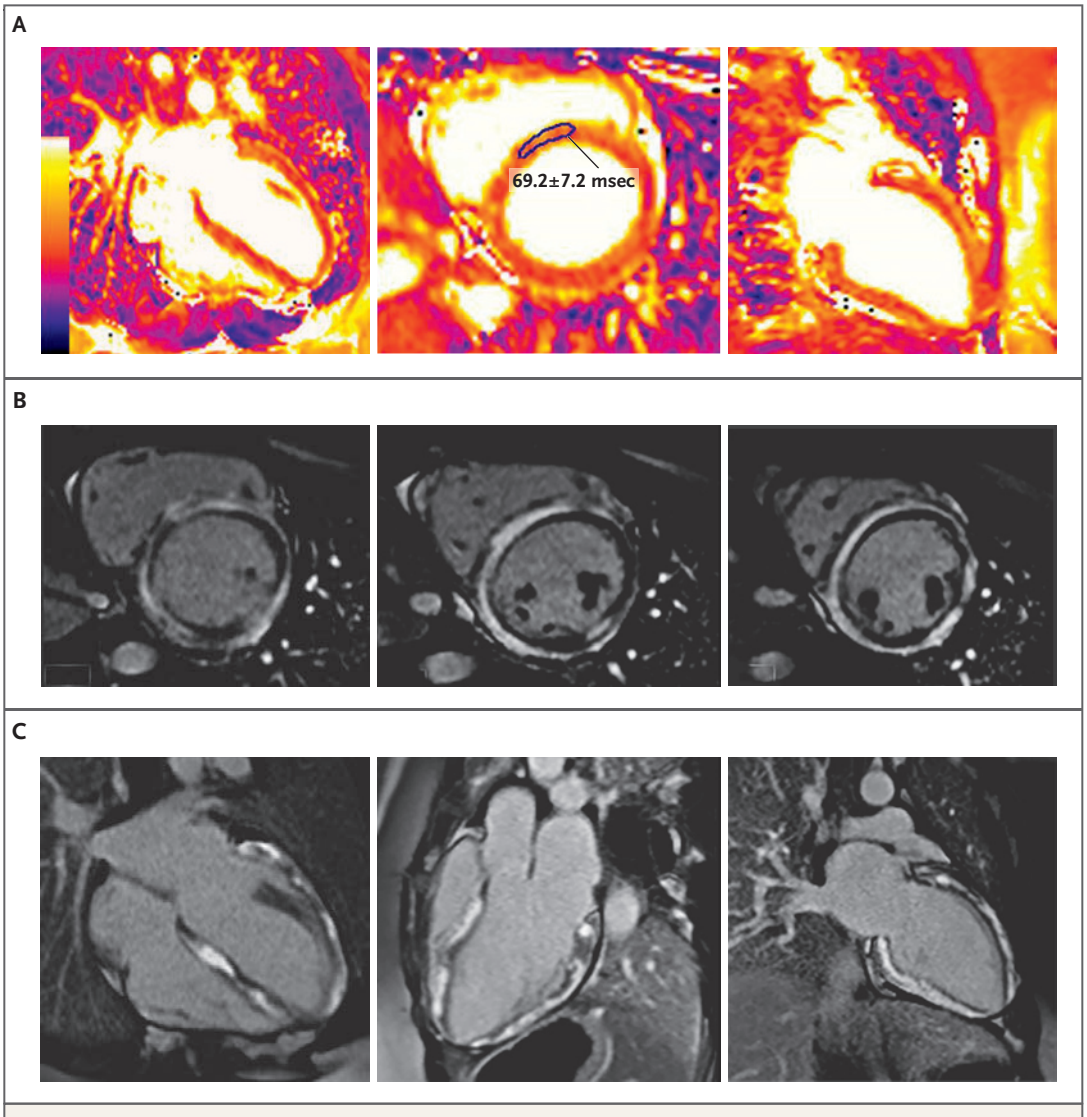

Figure 2. Cardiovascular MRI.

Myocardial T2 maps show diffuse patchy clinically significant elevation (67 to 75 msec; normal range, 42 to 48) (Panel A, four-chamber view [left], basal short-axis view [middle], and two-chamber view [right]). The plus–minus value is mean ±SD. Late post–gadolinium-contrast acquisitions show strikingly dense circumferential left ventricular epicardial and midwall late enhancement, reaching transmurality in places with involvement of the right ventricular septum (Panel B, basal and two mid left ventricular short-axis views; and Panel C, four-chamber view [left], three-chamber view [middle], and two-chamber view [right]). The full left ventricular short-axis stack is shown in Figure S1.

The amount and distribution of the myocardial edema and inflammation (T2 mapping images) and late gadolinium enhancement on cardiovascular MRI are impressive. The pattern is nonischemic and points to conditions such as acute myocarditis. Other possibilities include giant-cell myocarditis — which can also cause left ventricular systolic impairment, hypotension, and nonsustained ventricular tachycardia — or an acute necrotizing eosinophilic form of myocarditis, which has been described with the use of *G. cambogia*. Also possible is an acute phase of a genetic condition such as desmosomal arrhythmogenic cardiomyopathy or filamin and lamin cardiomyopathies, all of which are associated with a "ringlike" pattern of late gadolinium enhancement. Both filamin and lamin cardiomyopathies can manifest with arrhythmias, although there is no evidence of peripheral muscular involvement, which can be associated with both, and no conduction abnormalities or atrial arrhythmias, which are often associated with the latter. Cardiac sarcoidosis also cannot be ruled out, although the absence of extracardiac findings or bradyarrhythmias would be unusual with such a florid presentation. In view of the left ventricular systolic impairment and arrhythmias, an endomyocardial biopsy is indicated.

Given the nonsustained ventricular tachycardia, hypotension, and findings on cardiovascular MRI, giant-cell myocarditis was suspected, and empirical treatment was initiated with one dose of an intravenous glucocorticoid as well as bisoprolol, ramipril, and eplerenone. The patient's case was also discussed with the rheumatology and infectious diseases teams. Right ventricular endomyocardial biopsy was performed (after which treatment with the intravenous glucocorticoid was continued), and seven myocardial septal samples were obtained. Histopathological analysis showed mild reactive changes in myocytes and occasional interstitial lymphocytes not reaching criteria for a lymphocytic myocarditis (Fig. S2). There were no giant cells, eosinophils, neutrophils, or granulomas. There was minimal interstitial fibrosis. Immunostaining showed a few scattered CD3- and CD4-positive T cells. Staining for cytotoxic CD8-positive T cells and CD20-positive B cells was negative. There was no evidence of amyloid, iron, or storage deposition. PCR testing of a blood sample was negative for Epstein–Barr virus, and PCR testing of nasal swabs was negative for adenovirus, influenza A virus, and respiratory syncytial virus. Angiotensin-converting–enzyme levels were in the normal range. Tests for rheumatoid factor, extractable nuclear antigens, cardiac muscle antibodies, anticardiolipin antibodies, antimyeloperoxidase antibodies, and anti–proteinase 3 antibodies were negative.

False negative results of endomyocardial biopsy are possible in acute myocarditis, but the number of samples obtained from the right ventricle and the evidence of right ventricular septal involvement on T2 mapping images and of late gadolinium enhancement on cardiovascular MRI increase the sensitivity. The absence of giant cells and eosinophils rules out giant-cell myocarditis and eosinophilic myocarditis, respectively.

The patient's condition improved, with no further chest pain or arrhythmias and decreasing troponin levels, and the glucocorticoid was switched to oral administration with a scheduled taper. She was discharged with a plan for further outpatient testing and early follow-up in the clinic. A Holter monitor was fitted 10 days after hospital discharge after a telephone follow-up, during which the patient reported palpitations; it showed frequent ventricular arrhythmias with runs of nonsustained ventricular tachycardia of up to 210 beats per minute (Fig. S3). Oral amiodarone was initiated, which resulted in resolution of symptoms. ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET)–computed tomography (CT) showed no lymphadenopathies, no uptake of FDG in the lung parenchyma, and no large-vessel uptake, suggesting no active extracardiac sarcoid or large-vessel vasculitis. There was mild myocardial uptake, suggesting cardiac inflammation (Fig. 3).

Together with the suggestive pattern of late gadolinium enhancement, the normal ^{18}F-FDG PET–CT results and the presence of tachyarrhythmias increase the suspicion for an arrhythmogenic cardiomyopathy.

The inherited cardiac conditions team was consulted. The patient was reluctant to undergo genetic testing and did not wish to discuss clinical screening (as recommended with 12-lead ECG,

Figure 3. ^{18}F-Fluorodeoxyglucose Positron-Emission Tomography–Computed Tomography.
Mild myocardial uptake suggests ongoing cardiac inflammation.

echocardiography, and cardiovascular MRI) with her first-degree relatives.

Repeat cardiovascular MRI 12 months after the acute index presentation showed a mildly dilated left ventricle (end-diastolic volume, 104 ml per square meter of body-surface area; normal range, 65 to 99) with moderate global hypokinesia and focal thinning and akinesia of the basal and midinferolateral walls. The left ventricular ejection fraction (LVEF) was 39%. The right ventricle was normal in size with preserved function. Myocardial T2 values were still mildly elevated diffusely, in keeping with residual myocardial edema and inflammation. There was extensive subepicardial and midmyocardial late gadolinium enhancement, which was circumferential and extended from the base to the apex (Fig. 4A through 4C and Fig. S4). Levels of troponin and creatine kinase were normal.

In myocarditis, myocardial edema typically resolves within approximately 6 months after initial presentation. In contrast, repeat imaging in this case shows ongoing inflammation 1 year after the index admission.

After the repeat cardiovascular MRI showing persistent abnormalities, the patient consented to genetic testing. This revealed a frameshift variant (c.3639_364 deletion p. Glu1213AspfsTer2) in the gene encoding desmoplakin (*DSP*), which is predicted to cause premature protein truncation leading to loss of function and is pathogenic for arrhythmogenic cardiomyopathy (ClinVar ID, 1445018).

DSP encodes the desmoplakin protein, which plays a vital role in desmosomal cell adhesion. Loss-of-function variants are a known disease mechanism in arrhythmogenic cardiomyopathy. This variant has been classified as pathogenic with the use of the American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) guidelines for interpretation of sequence variants.

The diagnosis and associated risk of sudden cardiac death were discussed with the patient. After discussion at the meeting of the inherited cardiac conditions multidisciplinary team, placement of an implantable cardiac defibrillator was recommended for primary prevention (owing to the substantial amount and pattern of late gadolinium enhancement, her nonsustained ventricular tachycardia, and reduced ejection fraction). Benefits and risks were discussed, including the anticipated need for multiple generator changes given her young age, an associated risk of infection, and the risk of lead fracture; the patient has not yet made a decision. She was also given advice regarding avoidance of moderate-to-strenuous exercise, discontinuation of over-the-counter supplements, and family screening and was offered psychological support.

COMMENTARY

This 27-year-old woman presented with palpitations, chest pain, and elevated levels of cardiac enzymes with cardiovascular MRI showing marked diffuse cardiac inflammation with extensive circumferential nonischemic late gadolinium enhancement after taking a weight-loss pill and performing physical exercise. Sarcoidosis, giant-cell myocarditis, and necrotizing eosinophilic myocarditis were initially suspected but were ruled out by extensive investigations including endomyocardial biopsy and ^{18}F-FDG PET–CT. The ruling out of these conditions and the finding of late gadolinium enhancement led to genetic testing and the identification of a *DSP* mutation linked to arrhythmogenic cardiomyopathy and deemed to be pathogenic according to ACMG and AMP guidelines.[1]

Arrhythmogenic cardiomyopathy is a genetically determined myocardial disease that results from mutations in the genes encoding for

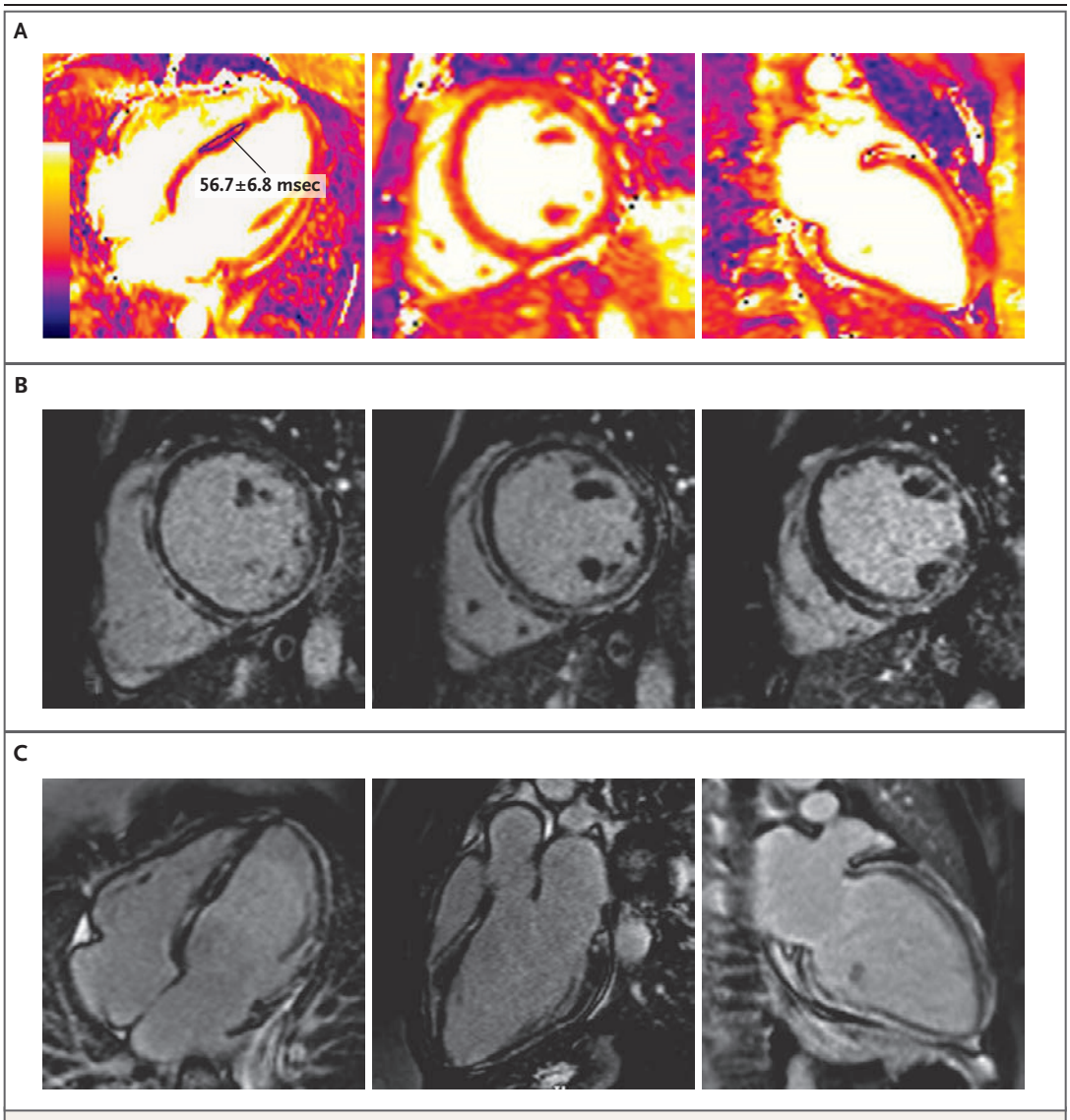

Figure 4. Cardiovascular MRI at 12 Months.

Myocardial T2 maps show persistence of mildly elevated values, which suggest residual myocardial edema or inflammation (Panel A, four-chamber view [left], basal short-axis view [middle], and two-chamber view [right]). The plus–minus value is mean ±SD. There was extensive subepicardial and midmyocardial late gadolinium enhancement, which was circumferential and extended from the base to the apex (Panel B, basal and two mid left ventricular short-axis views; and Panel C, four-chamber view [left], three-chamber view [middle], and two-chamber view [right]). The full left ventricular short-axis stack is shown in Figure S4.

desmosomal proteins.[2] Desmoplakin plays a vital role in desmosomal cell adhesion between cardiac myocytes, and loss-of-function variants are a known disease mechanism in arrhythmogenic cardiomyopathy. In particular, truncating *DSP* variants are responsible for a distinct form of arrhythmogenic cardiomyopathy characterized by myocardial inflammation, left ventricular fibrosis that precedes systolic impairment, and a high incidence of ventricular arrhythmias.[3]

The prevalence of the disease is estimated to be 1:2000 to 1:5000 in the general population. It can manifest at any age but most commonly manifests in early adulthood. In the past, arrhythmogenic cardiomyopathy was considered to be a right ventricular disease; however, left

ventricular involvement as well as a pure left dominant variant are now well recognized.[2] Typical symptoms relate to ventricular arrhythmias or ventricular dysfunction. However, some persons have acute chest pain and elevation of cardiac biomarkers, a clinical presentation that has been termed the "hot phase" and can mimic acute coronary syndromes and myocarditis.[4] In such cases, inflammatory infiltrates are commonly identified in autopsy findings and biopsy samples.[5,6] Inflammatory infiltrates are similarly reported in experimental animal models of arrhythmogenic cardiomyopathy,[7] although the activation of an innate immune response in cardiac myocytes that is independent of the actions of specific inflammatory cells has also been described.[8] Typically, when cardiomyopathy is not in a hot phase, biomarkers for myocardial damage are normal or near normal unless the patient has coexisting complications such as heart failure.[9]

Viral infections and physical activity have previously been reported to act as triggers for a hot-phase manifestation.[2] It is also possible that the diet pill contributed as a trigger in this case, acting in combination with exercise as a trigger. A previous report described the development of acute necrotizing eosinophilic myocarditis in a patient taking *G. cambogia*.[10]

The diagnosis of arrhythmogenic cardiomyopathy can be challenging. The most recent criteria for diagnosis are based on a multiparametric approach that involves myocardial functional and structural ventricular abnormalities, tissue characterization findings, ECG changes, and ventricular arrhythmias, as well as familial and genetic background.[2] In particular, they highlight the role of cardiovascular MRI as a fundamental imaging tool in the diagnosis, allowing tissue characterization, and focus attention on the left ventricular phenotype.[11]

Although the histologic hallmark of arrhythmogenic cardiomyopathy is fibro-fatty substitution, hot phases can occur. Inflammation, myocyte necrosis, and edema are characteristic features detectable by cardiovascular MRI.[4] During the hot phase, up to 50% of patients can show edema and late enhancement on late gadolinium enhancement sequences. With the increasing use of cardiovascular MRI, biopsy is not routinely performed to make a diagnosis, although it should be considered in patients who present with a myocarditis-like picture, to help differentiate between arrhythmogenic cardiomyopathy and other causes.[12]

As in our case, genetic testing can greatly contribute to diagnosis and risk stratification and should be considered in patients presenting with "acute myocarditis." In a recent study, genetic variants for dilated cardiomyopathy or arrhythmogenic cardiomyopathy were identified in 8% of patients with acute myocarditis, as compared with less than 1% of healthy controls.[13] Furthermore, a recent systematic review showed that 69% of patients with arrhythmogenic cardiomyopathy who presented with myocarditis-like episodes had *DSP* mutations.[14] In addition, a meta-analysis showed that among adult patients with complicated myocarditis who had acute heart failure, a reduced LVEF, or life-threatening ventricular arrhythmias, 21.9% had a pathogenic or likely pathogenic variant for cardiomyopathy-associated genes.[15]

This case serves as reminder that previously silent genetic conditions can manifest later in life, in some cases after an environmental "hit." It also highlights that genetic cardiomyopathies should be considered in the differential diagnosis of what appears to be acute myocarditis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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