42-Year-Old Woman With Bilateral Arm Tightness

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A 42-year-old woman presented to the emergency department (ED) with acute-onset crushing substernal chest pain that occurred while working in the hospital as a sign language interpreter. At 8:15 AM, she developed bilateral arm tightness and heaviness that subsequently radiated to her chest. The symptoms were associated with shortness of breath and nausea. She was urgently transported to the ED.

The patient disclosed a history of intermittent episodes of substernal chest pain dating back 9 years. Over the preceding 15 months she had increasing bouts of chest pain predominantly occurring in the early morning and lasting for up to 5 minutes with accompanied nausea and arm heaviness. She correlated her symptoms to the level of stress associated with current family and financial matters. One year ago, evaluation at an outside facility for a similar chest pain episode demonstrated normal cardiac enzymes and echocardiogram showed normal systolic and diastolic function. An exercise stress test was performed at that time with no symptoms reproduced during exercise or abnormal electrocardiographic findings.

Medical history included chronic headaches for which she took over-the-counter combination aspirin/acetaminophen/caffeine, ibuprofen, and less frequently hydrocodone/acetaminophen. She reported no association between the chest pain and her headaches. She denied a personal history of cardiac disease, hypertension, diabetes, hyperlipidemia, or depression. She was a current smoker and endorsed a 15-pack-year smoking history, but denied alcohol and illicit drug use. Her father died at age 65 years from a myocardial infarction.

Physical examination in the ED revealed a well-developed woman in moderate distress clutching at her chest. She was afebrile with a heart rate of 84 beats/min, blood pressure of 142/102 mm Hg without right-left arm discrepancy, and respiratory rate of 24 breaths/min. Oxygen saturation was 100% on room air, and the body mass index was calculated at 22.7 kg/m^2. No pallor, cyanosis, or diaphoresis was present. Precordial examination revealed a normal, nondisplaced point of maximal impulse, regular rate and rhythm, normal heart sounds without murmurs, rubs, or gallops. Chest pain was not reproducible. No jugular venous distension or carotid bruits were appreciated and peripheral pulses were normal, without lower extremity edema or calf tenderness. Bilateral breath sounds were equal, without wheezes or crackles. Abdominal examination was unremarkable.

At 8:26 AM, an electrocardiogram (ECG) upon arrival to the ED demonstrated approximately 1-mm ST-segment elevations in leads V1 to V4 and less than 1-mm horizontal ST-segment depression in leads II, III, and aVF.

1. Based on the patient's presentation, which *one* of the following is the *best* next step in management?

a. Urgent cardiac catheterization
b. Chest X-ray
c. Computed tomography (CT) with pulmonary embolism (PE) rule-out protocol
d. Intravenous lorazepam and morphine
e. Lipid panel

The patient's symptoms and ECG changes prompted ST-segment elevation myocardial infarction (STEMI) alert protocol. The patient received aspirin and ticagrelor, and a heparin drip was initiated in the ED rapidly. She was transferred to the cardiac catheterization laboratory at 8:39 AM.

Chest X-ray could certainly aid in ruling out other diagnoses. Information such as pulmonary edema, widened mediastinal silhouette, pneumothorax, pneumomediastinum, or a localized consolidation could suggest other etiologies. However, this should not delay

See end of article for correct answers to questions.

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reperfusion therapy for STEMI presentation. Although PE presents frequently with chest pain, the patient's substernal chest pain and ECG changes are more consistent with acute coronary syndrome (ACS). The patient smokes cigarettes and therefore meets 1 of the components of Virchow triad. However, her Wells score is low risk and she had no hypoxia, lowering PE on the differential diagnosis. Morphine, as opposed to aspirin, antiplatelet agents, nitrates, and oxygen, is uncommonly administered during the initial management of suspected STEMI. Morphine may have a deleterious effect on the action of dual antiplatelet therapy. Anxiolytics such as lorazepam are not a mainstay of treatment in this context. Anxiolytics could improve the patient's symptom-associated anxiety but should not delay the diagnosis of the underlying cause. Evaluation with a lipid profile should certainly take place during the hospital course, but in this setting urgent transfer to the cardiac catheterization suite for percutaneous coronary intervention (PCI) is a superior answer choice. Preprocedural laboratory evaluation should include complete blood cell count, creatinine, electrolytes, coagulation studies, and cardiac enzymes. Results demonstrating anemia, thrombocytopenia, or renal insufficiency would modify management decisions downstream such as anticoagulation choices, obtainment of blood products, or intravenous hydration before contrast studies. Likewise, cardiac enzymes serve a vital prognostic role.

As detailed above, the best answer choice for STEMI management is rapid transfer for catheterization because this is in accordance with the reperfusion goals established by the American College of Cardiology/American Heart Association guidelines. Reperfusion therapy should be undertaken as rapidly as possible, with a door-to-balloon time of 90 minutes in PCI-equipped centers and a door-to-needle (fibrinolytic therapy initiation) time of 30 minutes in non—PCI-capable centers.[1]

The chest pain subsided during cardiac catheterization and intraprocedural ECG demonstrated resolution of the ST-segment elevation without the administration of nitroglycerin. The procedure was completed at 8:56 AM and demonstrated normal coronary arteries without evidence of obstruction. Incidentally, before closure and femoral artery hemostasis device placement, a beading appearance along the femoral artery was seen during angiography.

2. Given the above-mentioned femoral angiography findings, clinical suspicion is significantly raised for which *one* of the following pathologic processes?

a. Atherosclerotic plaque deposition
b. Diffuse esophageal spasm
c. Pericarditis
d. Spontaneous coronary artery dissection (SCAD)
e. Stress-induced cardiomyopathy with or without apical ballooning

The appearance of STEMI due to atherosclerotic plaque appears as a complete or near-total obstruction of contrast dye flow through the target vessel. Likewise, the coronary artery catheterization was devoid of evidence of occlusive plaque, making this an incorrect answer choice. Diffuse esophageal spasm should be kept in mind in a patient presenting with chest pain. However, given our patient's ECG findings, ACS remains higher on the differential. Coronary angiography provides no information in the diagnosis of pericarditis, but rather results of an echocardiogram demonstrating pericardial effusion would be more informative. Furthermore, our patient's presentation is not typical of pericarditis, which would classically include pleuritic chest pain that changes with position, an auscultated friction rub, widespread ST-segment elevation, and PR-segment depression on ECG.

Beading along an artery is suggestive of segmental areas of alternating stenosis and aneurysmal outpouching. The classically described angiographic "string of beads" is seen in fibromuscular dysplasia (FMD).[2,3] Underlying vessel wall fibroplasia, hyperplasia, and microaneurysm predispose the affected arteries to spontaneous dissection. In a Mayo Clinic study of 87 patients with SCAD, there was an incidental diagnosis of FMD in 50% of patients (8 of 16) who underwent femoral angiogram before closure.[3] Stress-induced (takotsubo) cardiomyopathy can have a presentation similar to that of ACS. However, it is typically associated with left ventricular

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dysfunction and regional wall abnormalities, particularly at the apex. Symptoms and signs of left ventricular failure were not present in our patient, making this diagnosis unlikely. Takotsubo cardiomyopathy may be associated with apical ballooning, seen on both echocardiography and left ventriculogram.

Despite the femoral artery beading suggestive of possible FMD, coronary angiography demonstrated no evidence of SCAD, which is characterized by extravascular contrast sustainment (known as contrast hang-up) or segmental coronary narrowing, indicative of intramural hematoma on angiography. In select cases, intravascular ultrasound (IVUS) or optical coherence tomography are used to identify SCAD. In addition, cardiovascular magnetic resonance imaging may aid in the diagnosis of nonobstructive coronary artery disease (CAD) and can be helpful in differentiating pericarditis, myocarditis, microvascular disease, and ischemic myocardial disease.

In our patient, no contrast hang-up was seen on angiography and no evidence of SCAD was visualized on IVUS. Thus, coronary artery spasm remains the probable cause of the patient's chest pain.[3] Coronary artery spasm is also known as vasospastic angina (VA), variant angina, or Prinzmetal angina. Vascular smooth muscle spasm classically has an appearance of luminal narrowing and interrupted contrast dye flow on coronary angiography. Although the routine detection of coronary artery spasm may be challenging, it can be induced by drug administration or provocative maneuvers.[4,5]

The patient was transferred to the cardiology floor and monitored closely. The ACS protocol workup revealed an unremarkable complete blood cell count and metabolic panel, troponin T level of less than 0.01 on 3 occasions, and drug of abuse screen was negative for stimulants including cocaine. Chest X-ray demonstrated clear lung fields and normal cardiac silhouette. Echocardiogram demonstrated left ventricular ejection fraction of 68% with normal global and regional left ventricular systolic function and normal right ventricle. Electrocardiogram obtained after cardiac catheterization revealed normal sinus rhythm with resolution of the ST-segment changes. Of note, further diagnostic imaging with CT angiography was subsequently performed and ruled out fibromuscular dysplasia in renal, carotid, and vertebral arteries.

At 4:27 AM on hospital day 2, the Cardiology night team was called to the patient's room for an episode of 10/10 substernal chest pain with associated bilateral arm heaviness, which was identical to the previous episode. Vital signs were within normal limits and ECG demonstrated approximately 1.0-mm ST-elevations in the anterior leads with less than 1.0-mm horizontal ST-depression in the inferior leads, a similar pattern to the previous ECG. The patient's symptoms resolved spontaneously in less than 5 minutes. However, a second episode occurred while the care team was at the bedside. Sublingual nitroglycerin was administered and the pain resolved within 2 minutes. Repeat ECG following nitroglycerine administration demonstrated resolution of the ST-segment changes. The evaluation thus far had excluded obstructive coronary disease, nonatherosclerotic SCAD, stress-induced cardiomyopathy, pericarditis, and valvular heart disease. Furthermore, this episode of reversible symptoms and ECG changes with vasodilatory medications clinically confirmed the diagnosis of VA.

3. Based on the hospital course as detailed above, which *one* of the following is the *best* initial medication used to decrease exacerbations of this patient's condition?

a. Atorvastatin
b. Diltiazem
c. Isosorbide mononitrate
d. Propranolol
e. No medical therapy, observation alone

Statins have demonstrated promise as second-line or augmentative agents in treating VA. However, data exist from a small prospective study and have not been incorporated into widespread practice.[6] Statins have well-described pleotropic effects beyond their inhibition of cholesterol biosynthesis. Improvement in endothelial dysfunction is one of the mechanism theorized to play a role in reducing VA events.

Calcium channel blockers including nondihydropyridines and dihydropyridines are the first-line treatment in VA, with more than 90% of patients demonstrating response according to a Japanese observational study

across 11 centers that encompassed 286 cases.[7] Nitrates are also effective for the treatment of VA. However, concerns for nitrate tolerance and limited impact on the rate of long-term major cardiac events makes isosorbide mononitrate a second-line agent in treating VA.[8] Beta-blocking agents such as propranolol have been implicated in potentially exacerbating VA. Observation alone is an incorrect answer because a number of the above-listed agents have been shown to decrease long-term major cardiac events and reduce the frequency of vasospastic episodes.

Treatment with diltiazem was initiated and nitroglycerin sublingual tablets were prescribed as needed. The patient was monitored closely on cardiac telemetry into the late afternoon without any further episodes of angina. Her glycated hemoglobin, fasting lipid panel, and thyroid-stimulating hormone were measured and were normal.

4. In patients who are clinically suspected to have VA, the diagnosis can be confirmed by which *one* of the following tests?

a. Left ventriculogram during catheterization
b. Acetylcholine provocation test
c. Holter monitoring with event recording
d. Exercise or pharmacologic cardiac stress test
e. Hypoventilation provocation test

Coronary artery vasospasm (CAV) can cause an ischemic insult to the myocardium, leading to regional wall motion abnormalities or left ventricular dysfunction on a ventriculogram or echocardiogram. Wall motion abnormality, however, is nonspecific for VA and may also be visualized in atherosclerotic disease, heart failure, and stress-induced cardiomyopathy. Acetylcholine provocation testing during cardiac catheterization can help establish a definitive diagnosis of VA, and thus is the correct answer.[8,9] Our patient's clinical presentation of angina with transient ischemic ECG changes and supporting nonobstructive coronary angiogram, negative IVUS, and unremarkable left ventriculogram established the clinical diagnosis of VA. In cases less clearly defined, the Coronary Vasomotion Disorders International Study Group has established provocation testing as a diagnostic criterion.[10] Precipitation of coronary vasospasm leads to luminal narrowing, which confirms the diagnosis, but raises the potential for irreversible ischemic events and arrhythmias. Importantly, invasive provocation testing is associated with a less than 1% rate of periprocedural major cardiovascular adverse events based on a study of 239 women impacted by nonobstructive CAD who underwent such testing.[11] Holter monitoring or event recording with mobile cardiac outpatient telemetry may correlate ECG changes with angina and aid in the diagnosis of suspected VA. However, intracoronary acetylcholine provocation is a more specific diagnostic test, favoring pharmacologic provocation testing as the correct answer. Unlike angina caused by obstructive CAD, VA is not typically exercise-induced and the supply-demand mismatch is less dramatic. Therefore, cardiac stress tests serve a limited role in the diagnosis of VA. Provocation testing with hyperventilation (rather than hypoventilation) during coronary angiography has also been studied in the diagnosis of VA. However, the limited diagnostic accuracy of hyperventilation provocation test impedes its use as a confirmatory test for VA.[8,12]

Importantly, ergonovine provocation testing has also been studied in both an intracoronary and a systemic injection application. The European Society of Cardiology rates intracoronary ergonovine provocation testing as Level C, Class IIa Recommendation (in favor of treatment being useful/effective based on expert opinion, case studies, and standard-of-care) in 2013 updated guidelines.[13] The Japanese Circulation Society recommends that patients undergo acetylcholine or ergonovine provocation testing if cardiac catheterization is performed in the 2013 vasospastic angina guidelines.[12] In the United States, ergonovine is not approved by the Food and Drug Administration and its use remains off-label for the diagnosis of VA.

5. Which *one* of the following is the *best* treatment option for the patient's chronic headaches?

a. Smoking cessation
b. Sumatriptan
c. Ibuprofen
d. Acetaminophen
e. Aspirin

Tobacco and other stimulants (eg, cocaine) have been associated with triggering VA.

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However, smoking cessation is less likely to be the best treatment option for the patient's chronic headache.[4,8] Although our patient's chronic headaches were not formally diagnosed as migraine, she should be counseled to avoid medications such as triptans and nonsteroidal anti-inflammatory medications (NSAIDs) including ibuprofen. Both medications may exacerbate VA.[8] Neither acetaminophen nor opioids have been implicated in the exacerbation of VA, making acetaminophen the appropriate treatment option for the patient's headaches. At high doses, aspirin has been associated with worsening VAs, likely through a prostacyclin inhibitory mechanism.[8]

The patient was counseled on the importance of tobacco cessation and stress management, and to avoid the use of both stimulants and NSAIDs. These lifestyle modifications have all been demonstrated to be beneficial in reducing VA episodes alone or in combination with pharmacologic therapy.[3,4,8,12,14] Ultimately, she was discharged home with close follow-up in the Cardiology and Neurology-Headache clinics. Follow-up revealed a favorable response to diltiazem therapy with no recurrent chest pain episodes.

DISCUSSION

Heart disease is the most common cause of death worldwide, with approximately a third of individuals dying as a result of a myocardial infarction. Myocardial hypoperfusion typically occurs secondary to luminal narrowing often from a combination of atherosclerotic plaque, superimposed platelet fibrin thrombus, and coronary artery vasoconstriction. In this instance, ST-segment elevations on ECG indicate transmural myocardial ischemia warranting rapid reperfusion therapy. Other causes of ST-segment elevation on ECG include stress cardiomyopathy, coronary artery spasm, SCAD, and acute aortic dissection.[1,12,13]

Patients with newly identified ST-segment elevation should undergo an emergent cardiac catheterization, provided they are at a PCI-capable center, because decreased door-to-balloon time has been associated with beneficial outcomes.[1] In the interim, between ED arrival and PCI, several steps should be performed in a timely manner. Obtaining urgent basic laboratory testing and a portable chest X-ray is encouraged, as long as these diagnostic steps do not delay PCI. Echocardiogram before catheterization would unnecessarily delay intervention. Antiplatelet therapy (loading dose of aspirin and a thienopyridine) along with anticoagulation with unfractionated heparin should be initiated before cardiac catheterization.[1] No coronary artery stenosis was seen on our patient's coronary angiography, and thus other causes of chest pain and ST-segment elevation were considered. The clinical diagnosis of VA was established after other causes of ST-segment elevation were excluded.

Vasospastic angina occurs secondary to severe vasoconstriction of the epicardial coronary arteries, causing subtotal to total occlusion of the vessel with resulting acute, subacute, or chronic chest pain. In severe forms, VA can lead to myocardial infarction and sudden cardiac death.[8] Traditional risk factors for obstructive CAD are not necessarily implicated in this disease, though its underlying mechanism is not completely understood. Endothelial dysfunction, nitric oxide metabolite imbalances, and genetic predisposition are all theorized to contribute to the disease.[5] An inflammatory mechanism has been postulated because select studies have associated VA episode frequency to the level of C-reactive protein.[5,8] Last, disturbance of intracellular vascular smooth muscle calcium flow has been theorized because a small study demonstrated increased VA events in patients with magnesium deficiency, particularly alcoholics.[5]

Epidemiologic studies demonstrate that the disease is more common in Asian communities as compared with the Western world. Insufficient data are currently available to describe the disease incidence and prevalence in the United States.[4,8,12] Several risk factors are associated with VA including age, smoking, physical and emotional stress, use of stimulants, and medications such as β-blockers and sympathomimetics. Recurrent angina has been reported in nearly 12% of patients with VA and sudden cardiac death may occur in 0% to 10% of patients according to various studies.[4,8]

There are several clinical challenges involved in the diagnosis of VA. First, ST-segment elevations observed on ECG are more commonly associated with obstructive

CAD, given the significantly higher incidence of obstructive CAD over VA. Second, CAV is generally transient with quick recovery time, making the capture of unprovoked spasm on routine coronary angiography quite challenging. Third, confirming the diagnosis using provocative testing with hyperventilation or pharmacologic agents to induce spasm may be deferred at inexperienced centers or at those without the capability to administer intracoronary acetylcholine or ergonovine. Indeed, there may be hesitation on behalf of certain providers to definitively diagnose VA with provocation testing based on the fear that vasospasm induction could lead to severe angina, malignant arrhythmias, or irreversible myocardial damage.[4,9] However, as detailed above, provocation testing is safe and there have been no identified deaths attributed to such testing.[8,11] For these reasons, VA remains a potentially underdiagnosed cause for chest pain in many clinical practices.

Treatment of VA consists mainly of vasodilator medications. Calcium channel blockers are regarded as first-line therapy. The decision to select dihydropyridines or a nondihydropyridine agent can be tailored on the basis of patient's characteristics. Nondihydropyridine calcium channel blockers (eg, diltiazem and verapamil) are not recommended in patients with impaired systolic function. It is acceptable to combine 2 different calcium channel blockers as long as 1 of them does not have atrioventricular nodal blocking properties (eg, combining diltiazem and amlodipine). Short-acting nitrates, such as nitroglycerin, can be prescribed as rescue agents for anginal pain. Alternatively, longer-acting nitrates such as isosorbide mononitrate or transdermal nitroglycerin may also be used as second-line agents. Medications such as statins, antioxidants, and magnesium have been shown to improve chest pain in VA, but strong evidence is lacking to support their routine use.[6,15] It is important to avoid beta-blockers in patients with VA because they may cause unopposed alpha stimulation and therefore exacerbate coronary vasospasm.

Performing PCI with balloon angioplasty or stenting is controversial in VA. An ill-defined "skipping phenomenon" has been demonstrated during PCI in patients with VA, whereby coronary artery stenting induces spasm downstream or in another vessel. Therefore, PCI interventions are typically reserved for patients with comorbid obstructive CAD or who have intractable symptoms despite optimal medical therapy.[8,12] Similar to the question of revascularization, the use of implantable cardioverter devices (ICDs) to abort malignant arrhythmias caused by VA is also controversial. No randomized studies to date have investigated ICD placement in patients with VA.[4,8,13]

In conclusion, coronary artery vasospasm may cause severe angina symptoms that mimic ACS due to obstructive CAD. Because of diagnostic challenges, VA is often underdiagnosed. Evidence suggests that medical therapy along with numerous lifestyle modifications may alleviate or reduce the recurrence and intensity of this disease. No randomized controlled trials demonstrating a significant impact on the natural history of this disease exist to date.

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