

62-Year-Old Woman With Diarrhea, Vomiting, and Chest Pain

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See end of article for correct answers to questions.

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A 62-year-old woman presented to an outside emergency department with a 24-hour history of vomiting-associated chest pain. She described a nonradiating retrosternal ache with dyspnea and diaphoresis after multiple episodes of nonbilious and severe vomiting. Recent history was notable for amoxicillin/clavulanic acid-treated colitis. After failure to improve, she was diagnosed as having *Clostridium difficile* and completed 10 days of treatment with vancomycin. Two weeks prior to presentation, fidaxomicin was initiated because of persistent symptoms and ongoing stool positivity. Although there was initial improvement, decompensation occurred 24 hours prior to presentation, with 20 episodes of watery and bloody diarrhea. Medical comorbidities included hypertension and depression; she was a nonsmoker with no family history of heart disease. Home medications included escitalopram (10 mg daily), lisinopril (30 mg daily), and metoprolol tartrate (25 mg twice daily).

At presentation, she had sinus tachycardia with a heart rate of 100 beats/min but was otherwise hemodynamically stable with a blood pressure of 120/80 mm Hg. Cardiac examination revealed no murmurs, rubs, or gallops and normal jugular venous pressure (JVP). Lungs were clear on auscultation. Abdominal and rectal examination results were normal. Stool was positive for occult blood.

The patient underwent 12-lead electrocardiography (ECG) (Figure 1). Laboratory evaluation revealed the following (reference ranges provided parenthetically): hemoglobin, 12.4 g/dL (11.6 to 15.0 g/dL); white blood cell count, $14.2 \times 10^9/L$ (3.4 to $9.6 \times 10^9/L$); lipase, 61 U/L (13 to 60 U/L); C-reactive

protein, 0.62 mg/L (≤ 8.0 mg/L); alanine aminotransferase, 64 U/L (7 to 45 U/L); aspartate aminotransferase, 107 U/L (8 to 43 U/L); sodium, 133 mmol/L (135 to 145 mmol/L); potassium, 3.7 mmol/L (3.6 to 5.2 mmol/L); serum urea nitrogen, 6 mg/dL (6 to 21 mg/dL); and creatinine, 0.85 mg/dL (0.59 to 1.04 mg/dL). Her troponin I level was 0.90 ng/ml (< 0.034 ng/ml) at presentation and 1.75 ng/ml after 2 hours. She took 162 mg of aspirin prior to presentation.

1. Based on the clinical data presented, which one of the following is the most likely early diagnosis?
 - a. Esophageal rupture
 - b. Toxic megacolon
 - c. Non-ST-elevation myocardial infarction (NSTEMI)
 - d. Apical ballooning syndrome (ABS)
 - e. Acute pulmonary embolism (PE)

The clinical presentation of esophageal rupture may be vague, but the classic triad of symptoms includes severe vomiting followed by chest pain and subcutaneous emphysema. While not always the case, this scenario often occurs following overindulgence of food or alcohol.¹ This patient lacks subcutaneous emphysema and neither cardiac biomarkers nor ECG findings are congruent with this diagnosis. However, esophageal rupture is a frequently fatal condition that should be excluded on radiography or computed tomography (CT).

Toxic megacolon can occur in patients with recurrent *C difficile* infection. Typically, patients are systemically unwell with severe bloody diarrhea, abdominal pain, and distention. This patient had benign abdominal examination findings. Further, this diagnosis

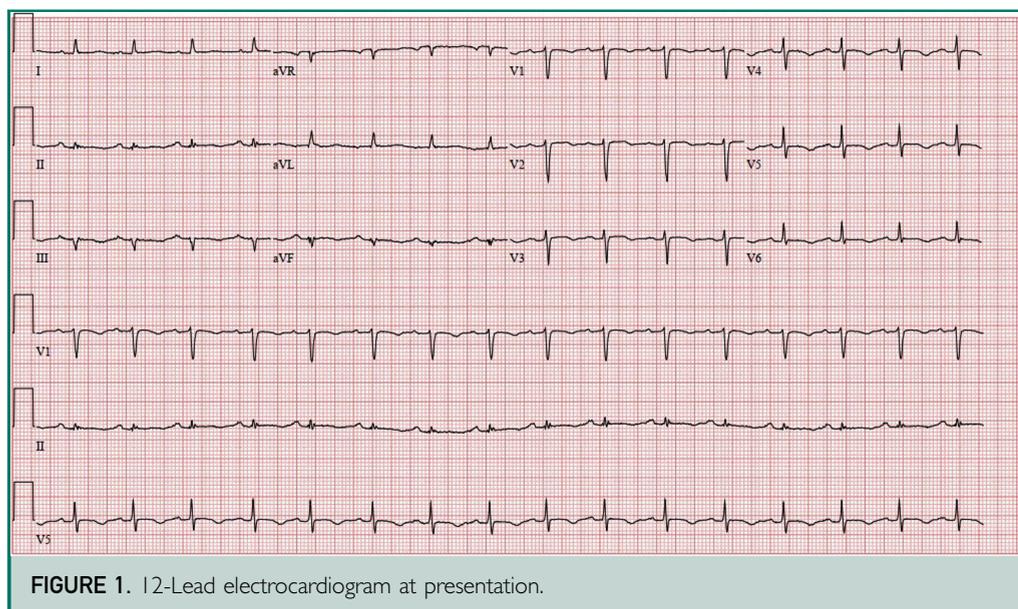


FIGURE 1. 12-Lead electrocardiogram at presentation.

does not explain the cardiac abnormalities seen in this case.

The ECG revealed relatively small QRS complexes with mild, nonspecific ST changes and T-wave inversion in the precordial leads. Retrosternal chest pain and rising cardiac biomarkers raise concern for non-ST-elevation myocardial infarction, although the patient does have relatively few risk factors. Apical ballooning syndrome, also known as Takotsubo syndrome, also mimics this presentation. While not always the case, ABS is often precipitated by an emotional or physical stressor.² This patient's chest pain occurred in the setting of severe vomiting and diarrhea, which may qualify as an inciting event. She also fits the demographic of a postmenopausal woman, in whom this condition is commonly seen.² While underlying obstructive coronary artery disease may be a more common etiology, ABS is a more compelling diagnosis in this case.

Cardiac troponins are frequently elevated in cases of PE and are associated with increased short-term mortality and adverse outcomes.³ Nonspecific ST-segment and T-wave abnormalities with sinus tachycardia may be seen on ECG. Other classic abnormalities such as the $S_1Q_3T_3$ pattern, right

axis deviation, and right bundle branch block are not as frequent. Abnormalities are best seen in patients with massive or submassive embolization, and ECG findings are typically unremarkable otherwise.⁴ Symptoms of acute PE include dyspnea, pleuritic chest pain, tachypnea, and hemoptysis. This clinical presentation likely favors an alternative diagnosis.

The patient underwent CT of the chest and abdomen with intravenous contrast medium, which revealed no acute vascular abnormalities, PE, or esophageal rupture. There was a small right pleural effusion with mild interlobular septal thickening and mild wall thickening of the sigmoid colon concerning for mild focal colitis. Incidentally noted was an enlarged multinodular goiter with numerous scattered calcifications. The patient's thyrotropin level was 0.05 mIU/L (0.3 to 4.2 mIU/L), and the free thyroxine concentration was 1.6 ng/dL (0.9 to 1.7 ng/dL).

2. Which one of the following is the best diagnostic test to perform next in the management of this patient?

- Colonoscopy
- Esophagogastroduodenoscopy
- Transthoracic echocardiography (TTE)

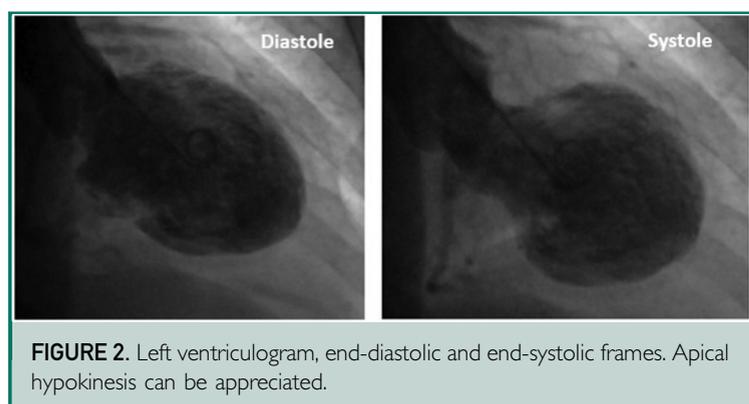


FIGURE 2. Left ventriculogram, end-diastolic and end-systolic frames. Apical hypokinesis can be appreciated.

- d. Coronary angiography
- e. Cardiac magnetic resonance imaging

A colonoscopy may be warranted for this patient given her refractory diarrhea and evidence of colitis on CT. However, the cardiac abnormalities deserve more immediate exploration, and colonoscopy is not the best next step in this case. This same logic applies to esophagogastroduodenoscopy, as the abnormal cardiac findings take precedence.

Transthoracic echocardiography is useful to detect regional wall motion abnormalities and assess left ventricular (LV) function. Characteristic wall motion abnormalities seen in ABS are hypokinesis or akinesis of the mid and apical LV segments. Visualization of the apex can be difficult with this imaging modality, particularly in patients who are acutely unwell.² Although TTE may still provide useful adjunctive information, urgent assessment of the coronary arteries is needed first in this patient to rule out acute coronary syndrome (ACS). Apical ballooning syndrome is a diagnosis made after exclusion of obstructive or occlusive coronary artery disease.

Coronary angiography should be performed in patients with possible ACS, particularly with elevated and evolving biomarkers. Given the significant degree of troponin elevation in this case, assessment of the coronary arteries is critical. Although typically normal in patients with ABS, obstructive atherosclerotic plaques may be seen in 10% of patients.⁵ Single-vessel obstructive lesions

do not exclude the diagnosis of ABS. Wall motion abnormalities typically extend beyond the distribution of a single coronary artery.^{2,5} The addition of left ventriculography allows for assessment of LV function and morphology once an acute coronary lesion has been excluded. Alternatively, TTE could also be performed at this stage.

Cardiac magnetic resonance imaging may be useful to assess the extent of a regional wall motion abnormality, particularly if TTE images are suboptimal or inconclusive.^{2,5} This modality would not, however, be the first-line imaging study. If definitive diagnosis remains unclear following catheterization, it may aid in differentiating between alternative diagnoses. If delayed gadolinium enhancement is seen, the more likely diagnosis would be myocarditis or myocardial infarction (MI) because this feature is absent in ABS.^{2,5} If present, the pattern of delayed gadolinium enhancement can also aid in distinguishing diagnoses. Myocardial infarction is more often associated with subendocardial delayed gadolinium enhancement, whereas myocarditis is associated with a subepicardial pattern.

Following transfer to our service, the patient's diarrhea resolved, with no further episodes of hematochezia. The patient's high-sensitivity cardiac troponin T level was 272 ng/L (≤ 10 ng/L) on arrival and 259 ng/L after 2 hours. Given her stable hemoglobin level and continued elevation in cardiac biomarkers, aspirin was administered and heparin infusion was initiated. Home antihypertensives were withheld. Coronary angiography revealed normal coronary arteries. Left ventriculography documented severe hypokinesis of the apical segment, and the calculated LV ejection fraction was 34% ($>50\%$ to 55%). Left ventricular end-diastolic pressure was 40 mm Hg (Figure 2).

Based on the presentation, ECG abnormalities, biomarker elevation, and angiographic findings, the diagnosis of ABS was made. Several hours after coronary angiography, the patient became increasingly tachycardic with heart rates up to 160 beats/min. She was dyspneic and hypoxemic with increasing oxygen requirements. She denied any recurrence of chest pain. Her blood pressure remained

stable. On examination, she was tachycardic and tachypneic with increased work of breathing. She had an elevated JVP and coarse breath sounds bilaterally.

3. Which one of the following is the most likely etiology for the patient's deteriorating condition?

- a. Thyrotoxicosis
- b. Ventricular wall rupture
- c. Severe mitral regurgitation
- d. Ventricular tachycardia (VT)
- e. Acute pulmonary edema

Sudden exposure to a large iodine load can overwhelm physiologic thyroid hormone regulation. A typical dose of iodinated contrast media contains approximately 10 times the recommended daily intake of iodine.^{6,7} A normal thyroid gland is usually able to adapt, although there have been cases of acute destructive thyroiditis following high-dose iodine in patients without preexisting thyroid disease.⁷ Another phenomenon is Jod-Basedow hyperthyroidism, whereby excess iodine is used as a substrate for new thyroid hormone synthesis. However, this disorder typically develops over 2 to 12 weeks in patients with either nodular thyroid or latent Graves disease. Our patient's multinodular goiter and suppressed thyrotropin level in the setting of these symptoms do raise concern. However, there are likely more compelling differentials involved in this case.

Ventricular free wall rupture is a devastating complication and most commonly manifests as sudden death with pulseless electrical activity. It may also present with symptoms of cardiac tamponade including tachycardia, hypotension, and elevated JVP. Patients typically experience sudden right-sided heart failure and cardiogenic shock, with rapid progression to electromechanical dissociation and death.⁸ This patient's blood pressure remains stable, making this diagnosis unlikely. Mechanical complications due to ABS are also exceedingly rare.^{2,9}

Mitral regurgitation can occur in ABS, whether due to leaflet tethering independent of LV outflow tract obstruction or with LV outflow tract obstruction with systolic

anterior motion of the mitral valve.^{9,10} This disorder also typically presents with symptoms of heart failure and cardiogenic shock. Although there is certainly concern for heart failure in this patient, she is not hypotensive, once again rendering this diagnosis less likely. We would also likely find a systolic murmur on cardiac examination.

The clinical presentation of VT is variable and dependent on rate and duration. If non-sustained, patients are often asymptomatic, but possible symptoms include palpitations, chest pain, dyspnea, presyncope, or syncope. Ventricular tachycardia is a rare complication of ABS, and this patient's worsening hypoxemia likely favors an alternative diagnosis. Electrocardiographic telemetry revealed sinus tachycardia with no evidence of VT.

Heart failure is the most common complication of ABS and occurs in approximately 20% of patients with this condition.² A proposed risk score to predict the likelihood of development of acute heart failure is based on 3 variables: (1) age greater than 70 years or (2) the presence of a physical stressor and (3) LV ejection fraction of less than 40%. The presence of 1, 2, or all 3 of these variables is associated with a risk of approximately 28%, 58%, and 85%, respectively.¹¹ Acute pulmonary edema triggered by heart failure due to LV systolic dysfunction is the most likely cause of this patient's symptoms and sudden change in clinical status.

Portable chest radiography and point-of-care lung ultrasonography confirmed the presence of pulmonary edema. The patient was transferred to the cardiac intensive care unit for ongoing management with noninvasive positive pressure ventilation and intravenous diuretics. She had rapid improvement in her respiratory status, and her tachycardia resolved.

4. In addition to β -blocker therapy, which one of the following medications is most appropriate to initiate at this stage?

- a. Angiotensin-converting enzyme inhibitor (ACEi)
- b. Aspirin
- c. Statin
- d. Clopidogrel
- e. Warfarin

There are many controversies regarding the management of ABS and no clearly established guidelines. If tolerated, β -blocker therapy is usually the first line of treatment, given that catecholamines are thought to play a role in the pathogenesis of disease.² Frequently, angiotensin-converting enzyme inhibitors (ACEis)/angiotensin receptor blockers are also used empirically as part of standard heart failure management.^{2,12} Apical ballooning syndrome is definitively confirmed after systolic function recovers, rendering this treatment regimen important in diagnosis.

Administration of aspirin at initial presentation is warranted. It can be discontinued if there is no evidence of coexisting atherosclerosis on cardiac catheterization.² Similarly, there is no indication for statin therapy in ABS in the absence of coronary atherosclerosis or without another indication. Clopidogrel would also not be indicated once the diagnosis of acute MI is excluded.

Warfarin should be considered in severe LV dysfunction for LV thrombus prevention. Left ventricular thrombus is rarely present in the acute setting; however, it would also certainly be an indication for anticoagulation.²

The patient was discharged from the hospital 5 days after presentation with a regimen of ACEi and β -blocker. She had no further vomiting or diarrhea during her hospitalization. She was referred to outpatient gastroenterology, where her *C difficile* infection was thought to be related to antibiotic use. Her symptoms subsided following treatment with fidaxomicin.

5. Which one of the following is the most likely outcome for this patient with ABS?

- Persistent LV dysfunction
- Slow improvement in LV function over months to years
- Recurrent ABS
- Long-term need for medical therapy
- In-hospital complication rates comparable to acute coronary syndrome

A predominant and defining characteristic of ABS is that it is a transient cardiomyopathy. Persistent LV dysfunction is not typical, and failure of LV recovery would

be highly suggestive of an alternative diagnosis. Recovery is relatively quick, rather than over prolonged periods such as months to years. Patients typically have full recovery of systolic function and wall motion abnormalities within 4 to 8 weeks.²

Although recurrence of ABS is a possibility, it is not the most likely outcome because only 1 in 10 patients will experience recurrence.² Long-term medication use is also not necessarily required. Some clinicians may elect to continue medical therapy; however, discontinuation may be considered after normalization of LV function.¹³

The most likely outcome is that although ABS does have a relatively good long-term prognosis, there is substantial risk of complications during the acute presentation. These complications include acute heart failure, as occurred in our patient with acute pulmonary edema, and stroke. Rates of in-hospital complications of ABS are comparable to those of ACS, and special vigilance should be taken to monitor for worsening heart failure, mental status changes, or changes on neurologic examination.¹⁴

As is typical for ABS, the patient's follow-up TTE at 6 weeks revealed complete normalization of LV function.

DISCUSSION

Apical ballooning syndrome is a reversible cardiomyopathy that mimics an ACS. The pathophysiology remains poorly understood, but given that the presentation is often precipitated by a physical or emotional stressor, catecholamine excess is thought to play a role in myocardial stunning.²

The Mayo Clinic criteria for ABS² are as follows: (1) a transient hypokinesis, akinesis, or dyskinesis of the LV mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always, present; (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac

troponin; and (4) absence of pheochromocytoma and myocarditis.

Although a transient condition, ABS is associated with substantial risk of adverse events similar to an acute MI. A large Mayo Clinic study comparing outcomes between ABS and acute MI revealed that at least one complication occurred in 38.2% of patients with ABS, compared to 32.6% in the acute MI cohort.¹⁴ The most common complications seen in ABS were acute heart failure and stroke.

β -Blockers tend to be the mainstay of treatment because of the proposed benefit of sympatholytic action. Angiotensin-converting enzyme inhibitors are also often used as part of the standard therapy regimen for heart failure.¹² There have been mixed reports with regard to overall benefit of these agents. The International Takotsubo Registry study revealed that the use of ACEis, but not β -blockers, was associated with survival benefit at 1 year from hospital discharge. Additionally, 30% of patients in this registry were taking a β -blocker prior to presentation, as were half the patients who experienced recurrence, suggesting that β -blockade does not reliably prevent recurrence.¹⁵ A subsequent analysis of long-term outcomes from the Mayo Clinic Takotsubo syndrome registry revealed that treatment with an ACEi or β -blocker was not associated with prevention of a recurrent event or prognosis.¹²

Apical ballooning syndrome is a serious condition and often precipitates acute heart failure syndrome. Further research is required to understand the underlying pathophysiology and best treatment practice for this disease.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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