CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 39-2017: A 41-Year-Old Woman with Recurrent Chest Pain

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PRESENTATION OF CASE

Dr. Mahesh K. Vidula (Medicine): A 41-year-old woman presented to this hospital with chest pain.

Approximately 1 year before presentation, the patient had had transient tightness in the chest and shoulder on the left side that had prompted a referral to outpatient physical therapy. Five days before presentation, while the patient was packing for a flight to Boston, acute substernal chest pain developed; the pain radiated to the jaw and shoulders and was accompanied by dyspnea and by a feeling of needing to belch. These symptoms lasted 1 hour and then spontaneously resolved, and she attributed them to fatigue.

On the day before presentation, substernal chest pain with radiation to the jaw and shoulders recurred after the patient had been walking, and the pain gradually resolved after a few hours. Before dinner on the evening of presentation, the pain recurred and was associated with light-headedness. The patient attended dinner but had persistent pain, along with dyspnea. She presented to the emergency department of this hospital.

On physical examination, the patient was diaphoretic. The temperature was 36.6°C, the heart rate 68 beats per minute, the blood pressure 143/87 mm Hg in both arms, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while she was breathing ambient air. She did not have carotid bruits or jugular venous distention, nor did she have cardiac murmur, rub, or gallop on auscultation. Her digits were hyperextensible. The rest of the examination was normal. Laboratory test results are shown in Table 1.

The patient had no history of dysrhythmia, heart-failure symptoms, trauma, or constitutional, respiratory, gastrointestinal, or neurologic symptoms. She had undergone a laparoscopy for an ovarian cyst, and she had had a miscarriage 1 month before this evaluation. She took no medications. Penicillin and sulfa drugs caused urticaria. She exercised four times weekly with an elliptical machine and walked her dog daily. She did not smoke tobacco or use illicit drugs; she consumed two

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Presentation	8 Hr after Presentation
Troponin T (ng/dl)	<0.03	0.03	0.21
Hemoglobin (g/dl)	12.0–16.0	13.1	
Hematocrit (%)	36.0–46.0	39.0	
White-cell count (per mm^3)	4500–11,000	7540	
Platelet count (per mm^3)	150,000–400,000	316,000	
Sodium (mmol/liter)	135–145	141	
Potassium (mmol/liter)	3.4–5.0	3.8	
Chloride (mmol/liter)	98–108	105	
Carbon dioxide (mmol/liter)	23–32	19	
Urea nitrogen (mg/dl)	8–25	15	
Creatinine (mg/dl)	0.60–1.50	0.91	
Glucose (mg/dl)	70–110	98	
Magnesium (mg/dl)	1.7–2.4	1.6	
Cholesterol (mg/dl)			
Total	<200		159
High-density lipoprotein	35–100		63
Low-density lipoprotein	<130		86
Triglycerides (mg/dl)	40–150		52
Glycated hemoglobin (%)	4.3–6.4		4.6

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for magnesium to millimoles per liter, multiply by 0.4114. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

alcoholic beverages per week. She had a healthy 11-year-old daughter. Her father had a history of hypertension, atrial fibrillation, and an embolic stroke. Her mother, brother, and sister had hypermobile Ehlers–Danlos syndrome: her mother had joint hypermobility and had received the diagnosis during her first pregnancy because of recurrent hip subluxations; her brother had joint hypermobility and spontaneous pneumothorax and bruised easily; and her sister had joint hypermobility and bruised easily. A maternal second cousin had died at 51 years of age from a cerebral aneurysm. Electrocardiography and cardiac imaging studies were performed.

Videos showing echocardiographic and angiographic studies are available at NEJM.org

Dr. Lucy M. Safi: Electrocardiography showed normal sinus rhythm and submillimeter downsloping ST-segment depressions in leads V_3, V_4, and V_5 (Fig. 1). The depressions had decreased in magnitude on electrocardiography performed 3 hours later and had fully resolved on electrocardiography performed 8 hours after presentation.

Transthoracic echocardiography showed overall normal left ventricular and right ventricular systolic function. There was a small, focal area of hypokinesis in the left ventricular inferolateral wall (see Videos 1 and 2, available with the full text of this article at NEJM.org). There was no clinically significant valvular stenosis, regurgitation, or pericardial effusion. Although there was increased mobility of the interatrial septum, a color Doppler study showed no evidence of a patent foramen ovale.

Dr. Brian B. Ghoshhajra: Posteroanterior and lateral chest radiography showed no abnormali-

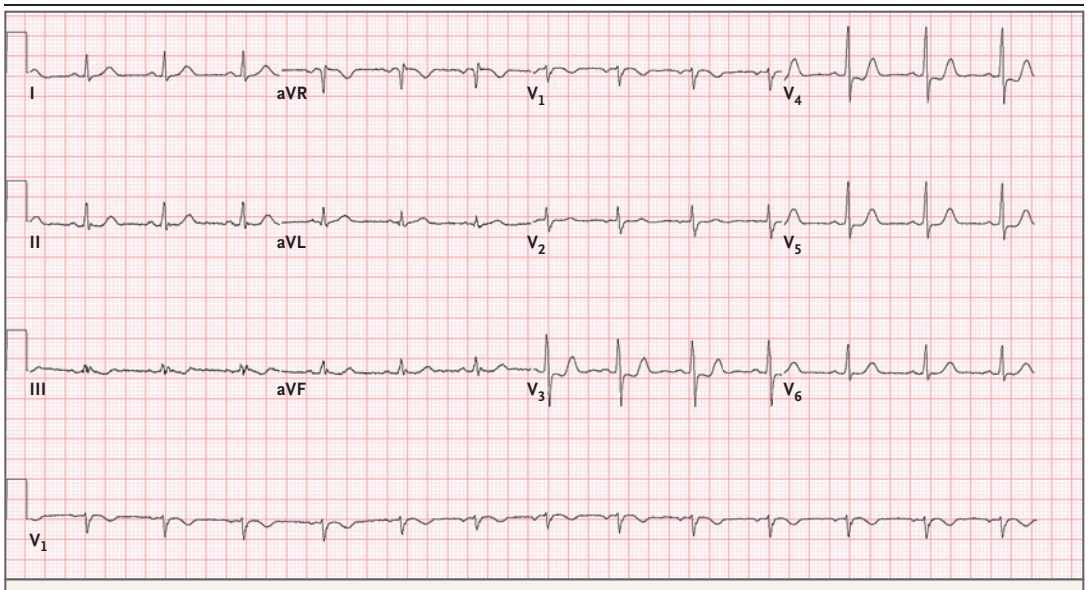

Figure 1. Electrocardiogram.

An electrocardiogram, which was obtained on presentation, shows a normal sinus rhythm and submillimeter downsloping ST-segment depressions in leads V_3, V_4, and V_5.

ties. Computed tomographic (CT) angiography of the chest was performed after the administration of intravenous contrast material with the use of a standard aortic-dissection protocol. There was no evidence of aortic dissection or proximal pulmonary embolism. The aorta appeared normal, with a preserved sinotubular junction, and the ascending aorta and descending aorta each had a normal diameter. There were no other obvious cardiovascular abnormalities, such as aortic or coronary atherosclerosis, cardiomegaly, or pulmonary edema.

Dr. Vidula: Aspirin, atorvastatin, and intravenous heparin were administered. Diagnostic tests were performed, and a diagnosis was made.

DIFFERENTIAL DIAGNOSIS

Dr. Sarah V. Tsiaras: This previously healthy 41-year-old woman, who had no history of a medical condition and no traditional cardiac risk factors, presented with acute chest pain that radiated to her jaw and shoulders and was associated with dyspnea and diaphoresis. Symptoms occurred transiently 5 days before presentation, recurred after exertion 1 day before presentation, and became persistent on the day of presentation.

The differential diagnosis of chest pain in a young woman is broad, but in this case, it can be narrowed quickly on the basis of the abnormal findings on electrocardiography, the hypokinesis in the left ventricular wall on echocardiography, and the acute elevation in the troponin level, findings suggestive of myocardial injury. In the presence of these findings, noncardiac causes of pain that are common in young women (e.g., gastroesophageal reflux disease, esophageal spasm, and musculoskeletal pain) are unlikely.

MYOPERICARDITIS

Could this patient's chest pain be due to myopericarditis? Myocarditis or myopericarditis can result in focal or global myocardial inflammation, necrosis, and dysfunction. Focal myocarditis is often suspected in patients who present with chest pain (which is sometimes associated with heart failure or a viral illness) and with evidence of an acute coronary syndrome on electrocardiography or laboratory testing and who do not have evidence of obstructive coronary artery disease on coronary angiography. The diagnosis can be confirmed with the use of cardiac magnetic resonance imaging.[1,2] A diagnosis of focal myocarditis would partially explain the patient's chest pain, focal wall-motion abnormality, and elevated troponin level. However, the

patient did not describe any antecedent viral illness, which might lead us to suspect myocarditis. It is also notable that her troponin level was near normal on presentation and rose to 0.21 ng per deciliter 8 hours later. In patients with myocarditis, the troponin level is typically elevated on presentation and stays the same or gradually decreases over a period of days.

Chest pain due to pericarditis is usually described as a sharp pleuritic pain that improves with leaning forward and worsens with lying down, and such pain was not present in this patient. In patients with pericarditis, electrocardiography typically shows diffuse, concave ST-segment elevations and PR-segment depressions rather than the isolated ST-segment depressions that were seen in this case.

PULMONARY EMBOLISM

Pulmonary embolism is often considered in patients who present with acute chest pain. The Wells' criteria help to establish whether the pretest probability of pulmonary embolism is low, intermediate, or high.[3] These criteria include an alternative diagnosis that is less likely than pulmonary embolism, clinical signs of deep-vein thrombosis, previous deep-vein thrombosis or pulmonary embolism, a heart rate higher than 100 beats per minute, surgery or immobilization within the previous 4 weeks, hemoptysis, and active cancer. This patient does not meet any of these criteria. Moreover, patients with pulmonary embolism have pleuritic chest pain more often than substernal chest pain that radiates to the jaw and shoulders. Evidence of strain on the right side of the heart on electrocardiography (i.e., a S1Q3T3 pattern, with prominence of the S wave in lead I and a Q-wave and T-wave inversion in lead III) may be consistent with a diagnosis of pulmonary embolism, but it is uncommon, and pulmonary embolism can be associated with many different abnormalities on electrocardiography, including sinus tachycardia, anterior T-wave inversions,[4] new right bundle-branch block, and new atrial fibrillation. An elevated troponin level can be seen in patients with a large pulmonary embolism due to strain on the right side of the heart; in such patients, one might expect to see McConnell's sign on echocardiography (i.e., hypokinesis at the base and middle of the right ventricle with relative sparing of the apex).[5] I would consider a diagnosis of pulmonary embolism to be unlikely in this patient.

VASOSPASM

Vasospasm of the coronary arteries can cause chest pain, most often when the patient is at rest. Vasospasm typically occurs for a period of 5 to 10 minutes, but when it is prolonged, it can result in myocardial injury. Chest pain related to vasospasm usually resolves with the administration of sublingual nitroglycerin. Electrocardiography can show ST-segment depressions or ST-segment elevations that mimic those seen with acute ST-segment elevation myocardial infarction. Patients who present with vasospasm often have other vasoactive diagnoses, such as migraine or Raynaud's phenomenon. This patient has neither of these conditions and there is no mention that her chest pain was responsive to nitrates; therefore, this diagnosis is unlikely.

TAKOTSUBO CARDIOMYOPATHY

Patients who have takotsubo cardiomyopathy, which is also known as stress-induced cardiomyopathy or the apical ballooning syndrome, often present with chest pain, changes on electrocardiography, and an elevated troponin level. Takotsubo cardiomyopathy most commonly occurs in postmenopausal women and is usually precipitated by an intense physical or emotional stressor. Electrocardiography most often shows ST-segment elevations or deep, symmetric T-wave inversions; echocardiography typically shows hyperkinesis at the base of the left ventricle and akinesis at the apex. Patients who present with symptoms and signs of takotsubo cardiomyopathy often undergo urgent coronary angiography, and the diagnosis is made after coronary obstruction is ruled out and ventriculography shows akinesis at the apex of the left ventricle. On the basis of the patient's age, the absence of an inciting event, and the presence of a small, focal wall-motion abnormality on echocardiography, takotsubo cardiomyopathy is an unlikely diagnosis in this case.

AORTIC DISSECTION

When this patient presented to the emergency department, aortic dissection was appropriately considered and CT angiography was performed. Although the patient had not previously received

a diagnosis of hypertension, which is seen in most patients with aortic dissection, she had a family history of hypermobile Ehlers–Danlos syndrome. Hypermobility is seen with several types of the Ehlers–Danlos syndrome, including the hypermobile, classical, and vascular types.[6] Vascular complications, such as aortic dissection, are common only with the vascular type (but have been reported with other types), and aortic-root dilatation can be seen with both the classical type and the hypermobile type.[7,8] Unless the patient had an aortic dissection with involvement of the coronary arteries, this diagnosis would not explain the dynamic changes on electrocardiography or elevated troponin level seen in this case.

ATHEROSCLEROTIC CORONARY ARTERY DISEASE

Atherosclerotic coronary artery disease should be considered in any patient who meets diagnostic criteria for acute myocardial infarction, including symptoms of ischemia, an acute elevation in the troponin level, and new ischemic changes on electrocardiography. However, I believe this diagnosis is unlikely in this patient. She has no traditional risk factors for atherosclerosis, and patients who present with premature coronary artery disease typically have a strong family history of the disease, a history of tobacco use, or a markedly elevated level of low-density–lipoprotein cholesterol.

SPONTANEOUS CORONARY-ARTERY DISSECTION

Several features of this case arouse suspicion for spontaneous coronary-artery dissection, which accounts for up to 30% of acute coronary syndromes that occur in women younger than 50 years of age.[9] In this patient, clinical features that are consistent with this diagnosis include the absence of traditional cardiac risk factors, a history of recent miscarriage, a family history of the Ehlers–Danlos syndrome, and hyperextensible digits on physical examination. Certain hormonal influences are thought to increase the risk of spontaneous coronary-artery dissection, because many patients receive the diagnosis during either late pregnancy or the early postpartum period. Although this patient was not pregnant or in the postpartum period, she had had a miscarriage 1 month before presentation, and the increased progesterone levels during that pregnancy could have led to increased fragility of the arterial media. In addition, her family history of hypermobility, spontaneous pneumothorax, and cerebral aneurysm raises the question of whether she and her family carry a genetic mutation that increases the risk of a coronary-artery dissection. In one series of patients with spontaneous coronary-artery dissection, nearly one third had hypermobility on presentation.[10] Risk factors for spontaneous coronary-artery dissection that this patient did not have include intense physical activity, emotional stress, fibromuscular dysplasia, and systemic inflammatory conditions.

In patients who are hemodynamically stable and have improving or resolved chest pain, the diagnosis of spontaneous coronary-artery dissection can be made with the use of cardiac CT angiography. In patients with unremitting chest pain or in those who have nondiagnostic results on cardiac CT angiography, invasive coronary angiography is often performed, but there is a risk that introduction of the catheter into the coronary artery will propagate the dissection. Because this patient had ongoing chest pain, I would recommend invasive coronary angiography. Given the distribution of the wall-motion abnormalities on echocardiography, I suspect that the patient had a spontaneous dissection in the left circumflex coronary artery.

Dr. David M. Dudzinski (Cardiology): Dr. Vidula, what was your impression when you evaluated this patient?

Dr. Vidula: Our differential diagnosis included spontaneous coronary-artery dissection, acute myocardial infarction due to plaque rupture, aortic dissection, pulmonary embolism, pericarditis, and vasospasm. Given her young age, the absence of atherosclerotic risk factors, and the family history of the Ehlers–Danlos syndrome, we thought that the most likely diagnosis was spontaneous coronary-artery dissection. To confirm this diagnosis, we performed coronary angiography.

CLINICAL DIAGNOSIS

Spontaneous coronary-artery dissection.

DR. SARAH V. TSIARAS'S DIAGNOSIS

Spontaneous coronary-artery dissection, most likely involving the left circumflex coronary artery.

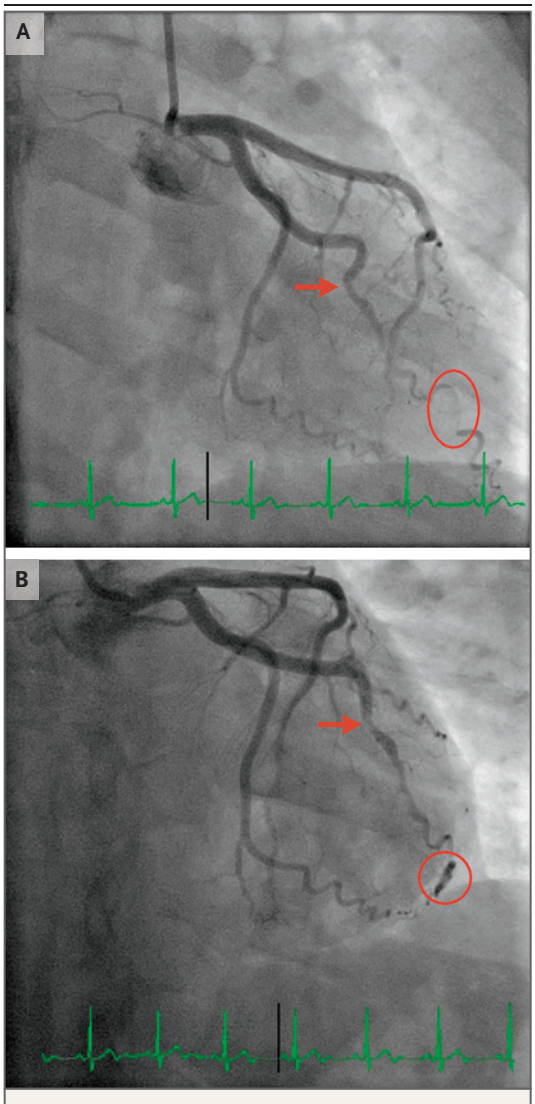

Figure 2. Coronary Angiogram.

An angiogram of the left coronary artery was obtained in the right anterior oblique caudal view (Panel A). Diffuse narrowing of the vessel lumen (arrow) and a filling defect (oval) are visible in the first obtuse marginal branch of the left circumflex coronary artery; these findings are consistent with an intimal tear and type 1 coronary-artery dissection. An angiogram of the left coronary artery was also obtained in the left anterior oblique caudal view (Panel B). Evidence of initiation of a coronary-artery dissection is visible in the first obtuse marginal branch, including narrowing of the vessel lumen (arrow) and staining of the vessel wall (circle); tortuosity of the coronary arteries is also shown.

DIAGNOSTIC TESTING

Dr. Malissa J. Wood: Catheterization of the left side of the heart and coronary angiography were performed. After injection of contrast material into the left main coronary artery (see Videos 3 and 4), a filling defect was identified in the first obtuse marginal branch of the left circumflex coronary artery (Fig. 2). There was evidence of sudden, diffuse narrowing of the vessel lumen and an irregular filling pattern, with preserved but delayed distal filling (Thrombolysis in Myocardial Infarction [TIMI] flow grade, 2 out of 3); these findings were consistent with coronary-artery dissection.

Coronary-artery dissection can be differentiated from atherosclerotic plaque rupture on the basis of the following features: the vessel wall is stained with contrast material and the lesion is longer and has a characteristic appearance. Coronary-artery dissection is frequently associated with the presence of excessive tortuosity of the coronary arteries. Distinct subtypes of spontaneous coronary-artery dissection have been described. Type 1 dissection, which was seen in this patient, is associated with a characteristic staining pattern within the vessel wall that is consistent with intimal disruption. Type 2 dissection is characterized by a diffuse, smooth pattern of luminal narrowing. Type 3 dissection, which mimics atherosclerosis, is associated with focal segments of luminal narrowing. Type 3 dissection is uncommon, and intravascular ultrasonography or optical coherence tomography may be performed to establish the diagnosis with certainty.[11]

Spontaneous coronary-artery dissection should be a strong consideration in a young woman or man who does not have traditional cardiac risk factors and who presents with an acute coronary syndrome. The initial evaluation should include electrocardiography and measurement of the troponin level, as well as echocardiography to evaluate for a possible wall-motion abnormality. Chest pain should be treated with sublingual nitroglycerin, and if there is no improvement, coronary angiography may be performed. In clinically stable patients who are pain-free and do not have evidence of ST-segment elevation, cardiac CT angiography may be considered.

DISCUSSION OF MANAGEMENT

Dr. Wood: After a coronary-artery dissection has been identified on coronary angiography, a conservative approach is typically warranted, particu-

larly in the presence of preserved distal perfusion. Placement of a guidewire for percutaneous coronary intervention can be technically difficult and can lead to abrupt vessel closure or propagation of the dissection.[12]

Currently, few data support the use of antiatherosclerotic medications in the management of spontaneous coronary-artery dissection. Most experienced clinicians support the use of low-dose aspirin (80 to 100 mg daily) in all patients with spontaneous coronary-artery dissection and the use of dual antiplatelet therapy in those who undergo percutaneous coronary intervention; thrombolytic therapy, long-term therapy with heparin, and therapy with glycoprotein IIb/IIIa inhibitors are otherwise typically avoided. Beta-blockers and angiotensin-converting–enzyme inhibitors may be used selectively in patients with ongoing angina or heart failure.[12,13] Statin therapy is not typically used for the treatment of spontaneous coronary-artery dissection but may be initiated in patients who have other indications.

Patients with spontaneous coronary-artery dissection are usually referred for cardiac rehabilitation. Unique cardiac-rehabilitation programs have been designed for this typically fit, young group of patients.[14] Because there is a frequent association between spontaneous coronary-artery dissection and fibromuscular dysplasia, CT angiography of the head, neck, abdomen, and pelvis is recommended. Genetic testing may be performed when there is a family history of possible connective-tissue disorders or evidence of connective-tissue disorders on physical examination or vascular screening; it may also be performed at the patient's request.[11-13] Given the features of this patient's presentation and the family history of the Ehlers–Danlos syndrome, we obtained additional imaging studies to rule out fibromuscular dysplasia and performed a genetic evaluation to determine whether an underlying genetic condition could explain her diagnosis.

IMAGING STUDIES

Dr. Ghoshhajra: CT angiography of the head, neck, abdomen, and pelvis was performed to evaluate for abnormalities of small and medium-sized vessels. The vessels in the head and neck were patent and had no evidence of aneurysm, dissection, or luminal irregularity, such as beading.

The arterial-phase abdominal images were slightly confounded by motion, but delayed-phase images showed multiple small, bilateral, wedge-shaped cortical defects that were consistent with remote renal infarctions (Fig. 3A and 3B). On arterial-phase abdominal and pelvic images, paired right and single left renal arteries were identified, all of which had subtle luminal irregularities (Fig. 3C and 3D), findings consistent with previous renal-artery dissections. However, there were no findings that would specifically suggest fibromuscular dysplasia, such as beading, stenosis, or aneurysm.

GENETIC TESTING

Dr. Mark E. Lindsay: It is common to perform a genetic evaluation in patients with spontaneous coronary-artery dissection because of the frequent absence of traditional cardiac risk factors in such patients and because of the known association of arterial dissection with genetic disorders. Genetic diagnoses associated with spontaneous coronary-artery dissection include Marfan's syndrome, the Loeys–Dietz syndrome, vascular Ehlers–Danlos syndrome, autosomal dominant polycystic kidney disease, and probably others.[10,15-18] In this case, the family history of hypermobile Ehlers–Danlos syndrome further motivated the genetic evaluation. In general, the Ehlers–Danlos syndrome is not associated with vascular features; however vascular Ehlers–Danlos syndrome (type 4), which is caused by disruption of the gene *COL3A1*,[19] is associated with nonaneurysmal arterial dissections.[20] Therefore, a primary goal of the genetic evaluation in this case was to discriminate specifically between a *COL3A1*–associated syndrome and nonvascular types of the Ehlers–Danlos syndrome.

Three first-degree family members had the Ehlers–Danlos syndrome, with symptoms including joint dislocations and hypermobility. However, the patient did not have joint dysfunction or objective hypermobility (i.e., she had a score of 0 on the Beighton scale of hypermobility, which ranges from 0 to 9, with a score >4 indicating generalized flexibility).[21] There was no family history of arterial dissection, hollow viscus rupture, sudden death, or emergency vascular surgery. In short, the family history was only superficially suggestive of vascular Ehlers–Danlos syndrome, and the patient did not appear to be affected by the familial joint condition. The ab-

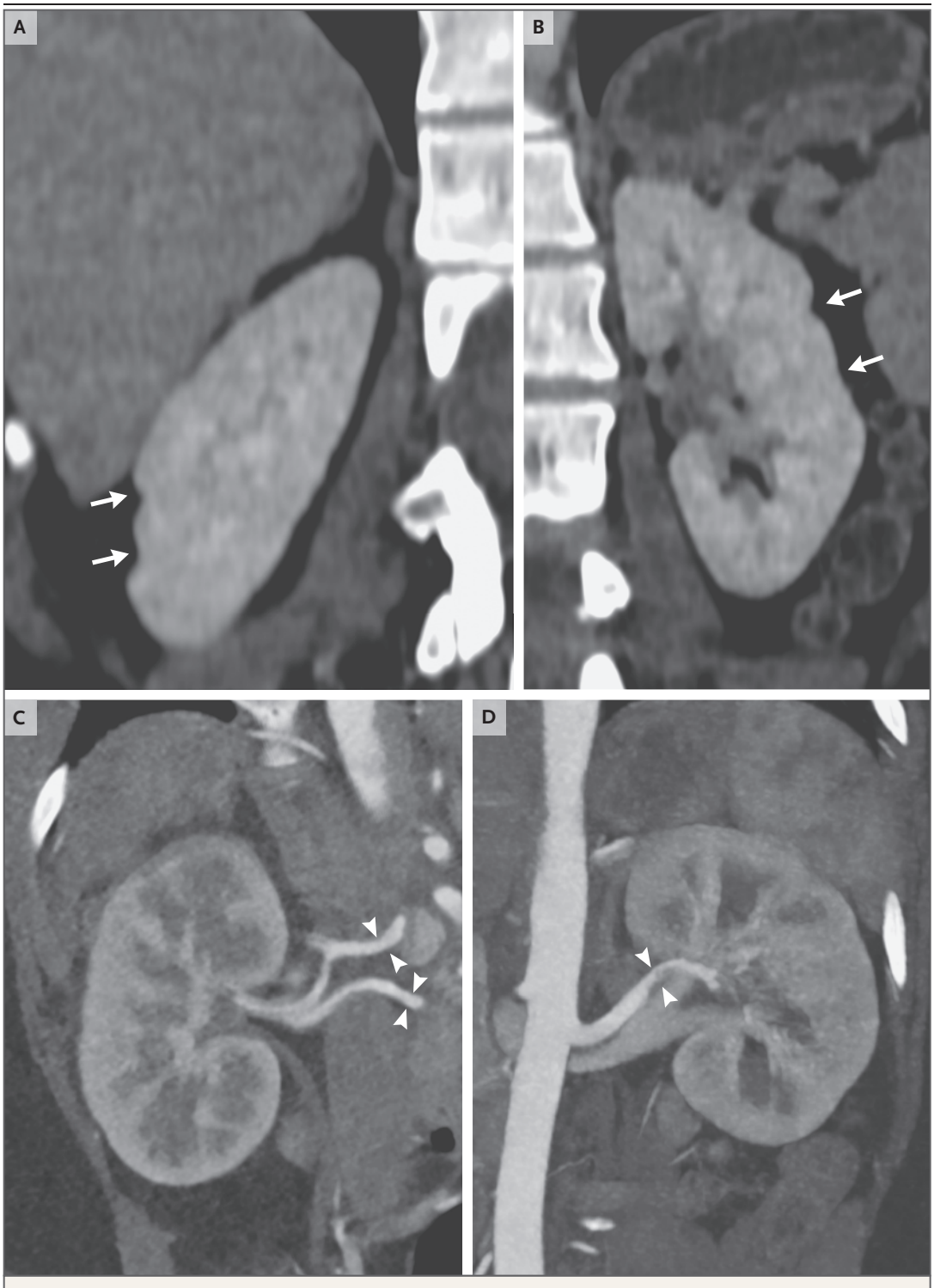

Figure 3. CT Angiogram.

Oblique coronal reformatted multiplanar images showing the long axis of the right and left kidney (Panels A and B, respectively) were obtained during the delayed phase. Bilateral, wedge-shaped cortical defects are visible (arrows); these findings are consistent with small, remote infarctions. Oblique coronal maximum-intensity-projection images showing the right and left renal arteries (Panels C and D, respectively) were obtained during the arterial phase. Paired right and single left renal arteries have subtle luminal irregularities (arrowheads).

sence of proximal aortic enlargement and the presence of noncystic kidneys on imaging studies in this patient reduced the likelihood of Marfan's syndrome, the Loeys–Dietz syndrome, or autosomal dominant polycystic kidney disease. A further consideration in this case was the absence of fibromuscular dysplasia. Monogenic vascular syndromes have not been found to be associated with a vascular morphology that is characteristic of fibromuscular dysplasia[22,23]; therefore, the absence of fibromuscular dysplasia in this case somewhat increases the probability of an identifiable genetic disorder.

Neither the examination nor the family history was suggestive of vascular Ehlers–Danlos syndrome, but external inspection alone cannot completely rule out this diagnosis, and the abnormalities of the renal arteries suggested a widespread arteriopathy. Given the patient's risk profile and her desire to assess familial risk, we recommended molecular genetic testing. After formal genetic counseling was provided and written informed consent was obtained, a blood sample was obtained for testing with a comprehensive panel of genes associated with aortopathy. The testing included sequencing and deletion and duplication analysis of 23 genes reportedly involved in arterial disease, including *COL3A1* (associated with vascular Ehlers–Danlos syndrome), *FBN1* (associated with Marfan's syndrome), and *TGFBR2* and *SMAD3* (associated with the Loeys–Dietz syndrome).[10,15-17] The test results, which were returned 2 weeks later, were negative. Given this patient's negative family history, unrevealing physical examination, and negative genetic testing, the possibility of a described mendelian vascular condition appears to be unlikely.

Dr. Wood: On follow-up treadmill stress testing 6 weeks after presentation, the patient was able to exercise for 9 minutes. There were no diagnostic changes on electrocardiography, and she did not have chest pain. Since the time of the follow-up evaluation, she has had fleeting episodes of intermittent chest pain but no prolonged episodes. She exercises daily, feels well overall, and continues to receive a low-dose beta-blocker, aspirin, and isosorbide mononitrate.

FINAL DIAGNOSIS

Spontaneous coronary-artery dissection.

This case was presented at the Medical Case Conference.

Dr. Ghoshhajra reports receiving consulting fees from Medtronic and Siemens Healthcare. No other potential conflict of interest relevant to this article was reported.

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

REFERENCES

1. Dec GW Jr, Waldman H, Southern J, Fallon JT, Hutter AM Jr, Palacios I. Viral myocarditis mimicking acute myocardial infarction. J Am Coll Cardiol 1992;20:85-9.
2. Monney PA, Sekhri N, Burchell T, et al. Acute myocarditis presenting as acute coronary syndrome: role of early cardiac magnetic resonance in its diagnosis. Heart 2011;97:1312-8.
3. Hendriksen JM, Geersing GJ, Lucassen WA, et al. Diagnostic prediction models for suspected pulmonary embolism: systematic review and independent external validation in primary care. BMJ 2015; 351:h4438.
4. Hariharan P, Dudzinski DM, Okechukwu I, Takayesu JK, Chang Y, Kabrhel C. Association between electrocardiographic findings, right heart strain, and short-term adverse clinical events in patients with acute pulmonary embolism. Clin Cardiol 2015;38:236-42.
5. McConnell MV, Solomon SD, Rayan ME, Come PC, Goldhaber SZ, Lee RT. Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. Am J Cardiol 1996;78: 469-73.
6. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet 2017; 175:8-26.
7. Bowen JM, Sobey GJ, Burrows NP, et al. Ehlers-Danlos syndrome, classical type. Am J Med Genet C Semin Med Genet 2017;175:27-39.
8. Tinkle B, Castori M, Berglund B, et al. Hypermobile Ehlers-Danlos syndrome (a.k.a. Ehlers-Danlos syndrome Type III and Ehlers-Danlos syndrome hypermobility type): clinical description and natural history. Am J Med Genet C Semin Med Genet 2017;175:48-69.
9. Tweet MS, Gulati R, Hayes SN. What clinicians should know about spontaneous coronary artery dissection. Mayo Clin Proc 2015;90:1125-30.
10. Henkin S, Negrotto SM, Tweet MS, et al. Spontaneous coronary artery dissection and its association with heritable connective tissue disorders. Heart 2016; 102:876-81.
11. Saw J, Aymong E, Sedlak T, et al. Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. Circ Cardiovasc Interv 2014;7:645-55.
12. Tweet MS, Hayes SN, Pitta SR, et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. Circulation 2012;126:579-88.
13. Tweet MS, Gulati R, Hayes SN. Spontaneous coronary artery dissection. Curr Cardiol Rep 2016;18:60.
14. Chou AY, Prakash R, Rajala J, et al. The first dedicated cardiac rehabilitation program for patients with spontaneous coronary artery dissection: description and initial results. Can J Cardiol 2016;32: 554-60.
15. Fattori R, Sangiorgio P, Mariucci E, et al. Spontaneous coronary artery dissection in a young woman with Loeys-Dietz syndrome. Am J Med Genet A 2012;158A: 1216-8.
16. van der Linde D, van de Laar IM, Bertoli-Avella AM, et al. Aggressive cardiovascular phenotype of aneurysms-osteoarthritis syndrome caused by pathogenic SMAD3 variants. J Am Coll Cardiol 2012;60:397-403.
17. Adès LC, Waltham RD, Chiodo AA, Bateman JF. Myocardial infarction resulting from coronary artery dissection in an adolescent with Ehlers-Danlos syndrome type IV due to a type III collagen mutation. Br Heart J 1995;74:112-6.
18. Grover P, Fitzgibbons TP. Spontane-

ous coronary artery dissection in a patient with autosomal dominant polycystic kidney disease: a case report. J Med Case Rep 2016;10:62.
19. Superti-Furga A, Gugler E, Gitzelmann R, Steinmann B. Ehlers-Danlos syndrome type IV: a multi-exon deletion in one of the two COL3A1 alleles affecting structure, stability, and processing of type III procollagen. J Biol Chem 1988; 263:6226-32.
20. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers–Danlos syndrome type IV, the vascular type. N Engl J Med 2000;342:673-80.
21. Beighton P, Solomon L, Soskolne CL. Articular mobility in an African population. Ann Rheum Dis 1973;32:413-8.
22. Poloskey SL, Kim ESH, Sanghani R, et al. Low yield of genetic testing for known vascular connective tissue disorders in patients with fibromuscular dysplasia. Vasc Med 2012;17:371-8.
23. Ganesh SK, Morissette R, Xu Z, et al. Clinical and biochemical profiles suggest fibromuscular dysplasia is a systemic disease with altered TGF-β expression and connective tissue features. FASEB J 2014; 28:3313-24.