A 67-Year-Old Man With Increasingly Frequent Angina

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Case Presentation

Present Medical History

A 67-year-old white man presented to Hermann Hospital upon referral from an Austin, Tex, physician for evaluation of recurrent chest pain. Eighteen months before admission the patient first noted episodes of chest discomfort, which he described as a left parasternal sensation of heaviness or tightness variably associated with moderate physical exertion. The discomfort would last 3 to 4 minutes and resolved with rest. He experienced one or two episodes each month. Two months before admission, an exercise stress test was performed and demonstrated 1.0 mm of "flat ST-segment depression" in leads II, III, aVF, and V5, through V6 at peak exercise (Bruce protocol; stage IV, 10 minutes). He experienced no pain during the test, and the ECG changes resolved within 30 seconds of stopping exercise. Five days before admission, the episodes of pain increased markedly in frequency, occurred several times a day, were provoked with only minimal exertion, and occurred at rest. He also noted episodes of left arm pain, with or without chest pain, which would last 30 to 60 minutes.

He was pain-free on admission. He denied any associated nausea, vomiting, diaphoresis, palpitations, dyspnea, orthopnea, edema, or fatigue. He reported no other symptoms.

Past Medical/Surgical History

The patient had a history of hypercholesterolemia (peak measured cholesterol was 225 mg/dL) and no history of hypertension or diabetes mellitus. Appendectomy, tonsillectomy, and knee surgery had been performed in the remote past. The patient’s father had a heart attack at age 79.

Medications

The patient took enteric-coated acetylsalicylic acid 325 mg daily and applied a nitroglycerin patch (formulation unknown) daily. He was allergic only to penicillin.

Social History

The patient is a retired university president and investment banker. He is married with two adult children who are healthy. He has one sibling who has no history of known heart disease. He smoked cigarettes occasionally during young adulthood, but quit at age 40. He drinks at least three cups of coffee each day but does not drink alcohol or use drugs except as prescribed by his doctor.

Physical Examination

The patient was of medium build, healthy, and in no distress. Vital signs were: temperature, 98.8°F; pulse, 76 beats per minute; blood pressure, 140/70 mm Hg; and respirations, 14 per minute. No abnormalities were noted in examination of the head, eyes, ears, nose, and throat; fundi appeared normal. The neck was supple; jugular vein pulse was 5 cm H2O; carotid upstrokes were brisk, of normal intensity, and symmetrical; no thymomalpaly or lymphadenopathy was noted. The chest was clear to auscultation bilaterally. Cardiovascular examination showed regular rate and rhythm: S1 and S2 were normal. An S3 was present, but no S4 murmur or rub was heard, and the point of maximal impulse was nondisplaced. The abdomen was soft and nontender, with normal bowel sounds and no hepatosplenomegaly. Genitourinary/rectal examination showed no palpable masses, a normal sphincter tone, and stool Guaiac negative. No skin lesions, edema, cyanosis, or clubbing was present in the extremities; pulses were brisk and symmetrical throughout. No neurological abnormalities were noted. Urinalysis showed normal chemistries and microscopic analysis. Anteroposterior chest radiograph showed prominent hilar vessels, cardiac silhouette of normal contour but indeterminate size, and no infiltrate or effusion present. The ECG showed sinus bradycardia (rate, 58 beats per minute); axis, 30°; normal wave morphology; and no ST-segment or T-wave abnormalities.

Laboratory Studies

Serum chemistries were Na,140;K, 4.4; Cl, 111; CO2, 23; Glu, 101; Cr, 1.0; BUN, 12; UA, 7.3; TP, 7.8; Alb, 4.3; Ca++, 9.3; Phos, 3.5; Chol, 223; TG, 260; ALT, 24; AST, 21; APHOS, 59; LDL, 136; and HDL, 35. Hematologic data showed WBC, 8.8; Hgb, 15.9; Hct, 46.7; MCV, 85.6; Plt, 303 000; and 69P/5bands/20L/4M/1B/1E. PT/PTT was 11.6/26.6.

Hospital Course

The patient was admitted to the coronary care unit for intensive monitoring, placed at bed rest, and started on an enteric-coated acetylsalicylic acid, intravenous nitroglycerin (NTG) at 5 µg/min and heparin at 1000
U/h IV (which was titrated to achieve a partial thromboplastin time of 60 to 80 seconds). Serial creatine kinase levels at 6-hour intervals were 64 U/L, 44 U/L, and 35 U/L, and isoenzyme measurements were not pursued. Thyroid function studies were within normal limits. About 18 hours after admission, he complained of mild to moderate retrosternal chest discomfort without radiation or other associated symptoms that lasted 10 minutes and resolved after an increase in the NTG infusion rate. No changes were seen on a stat ECG (per CCU fellow’s report). Two hours later, the patient’s heart rate was 48 beats per minute, and he felt dizzy. Symptoms resolved with administration of intravenous fluids and after decrease in the NTG infusion rate. An ECG revealed no acute ST-segment or T-wave changes (Fig 1). Subsequently, he had no further chest pain and his vital signs were stable (pulse average 68 beats per minute). Diltiazem was added on the third hospital day. A diagnostic procedure was performed on the fifth hospital day.

**Case Presentation**

The clinical picture presented to us at the outset of this Clinical Pathological Conference (CPC) points toward the syndrome of coronary ischemia manifest as mild, stable angina pectoris, which became quite unstable several days before hospital admission. It is our job to determine if indeed this is the case and, if so, the pathogenetic possibilities. In this instance, all roads appear to lead to coronary atherosclerosis, which might be reasonably expected to be present in a 67-year-old white male. Because it is very important to declare one’s point of departure early in the analysis of a clinical problem, we will start from that point. I liken this process to a mystery story. There often are clues in the first chapter, but the final answer comes many chapters later. Since this is a CPC, the obvious is usually not the answer, so I will try to extract the clues in the sequence presented, beginning with the history and physical examination.

**Clinical History**

A 67-year-old white male in apparent good health presents with an 18-month history of substernal tightness or heaviness initially noticed with moderate exertion but always relieved by rest after several minutes. There is no reported history of dyspnea on exertion (an anginal equivalent) or a change in stamina or energy manifest as fatigue, which commonly precedes the onset of angina pectoris if coronary atherosclerosis is involved. His exercise habits are not described nor is the type of exercise that initiates this discomfort mentioned. It is only in the 5 days before admission that rest chest tightness developed coincident with a rapidly increased frequency of exertional chest tightness consistent with an unstable anginal syndrome. The pain symptoms appear consistent and reproducible and were never described as sharp, pleuritic, variable in location, or related to body motion as one might expect with a pleural or musculoskeletal syndrome. There is no report of palpitation, tachypnea (palpitations in the left lateral decubitus position usually manifest best when lying in bed), or any central nervous system symptoms suggesting a change in cerebral blood flow pattern. Drug use was denied. Radiation of the chest discomfort was not documented until late in the course when left arm pain, with or without chest symptoms, developed. We are not told that he has any gastrointestinal symptoms such as heartburn, indigestion, eructation, epigastric discomfort, or history of gallbladder disease or dysphagia. There is no reason to believe that the enteric-coated acetylsalicylic acid played any causative role in the symptoms, especially since it was likely this medication was initiated after the onset of symptoms. We do know he was using a nitrate patch daily, but we do not know the duration or use. We do know his symptoms pro-
gressed despite the patch. No mention is made of the use of sublingual nitroglycerin or, if so, its effect.

We have no history of systemic symptoms such as weight loss, anorexia, fever, or malaise that might point to a malignancy or vasculitis as a causative factor in coronary ischemia, and there is no history of diabetes or hypertension. Although he had mild hypercholesterolemia in the past (225), he had no other significant general history of risk factors pointing to cardiovascular disease. His serum lipid analysis is reported later. He has not smoked in 27 years, and there is no family history of cardiovascular disease except for a father who had a myocardial infarction (MI) at the age of 79.

At this point, I believe we have sufficient direction from the history to stay with our original supposition that an anginal syndrome has now become unstable. The information obtained from careful and thorough history should satisfy the requirements of the first chapter of our mystery.

Physical Examination

As is often the case when patients with coronary ischemia are examined, there are few physical findings except in the presence of an MI when a systolic murmur of acute mitral regurgitation or ventricular septal defect may appear: an S₃, accompanying left ventricular (LV) dysfunction, a left parasternal systolic lift of pulmonary hypertension or acute left atrial enlargement, or rales of pulmonary congestion. However, in our case, the most common finding associated with coronary ischemia is described: an S₃. An S₃ is not to be confused with a split S₁ or an aortic or pulmonary valve opening sound, which may occur in the presence of mild or moderate aortic valve or pulmonic valve stenosis. An S₃ commonly signifies diminished compliance of the left or right ventricle resulting from myocardial hypertrophy or fibrosis. On the left side it may accompany any pathology producing LV outflow obstruction (aortic valve stenosis, idiopathic hypertrophic subaortic stenosis, supra- or infra-aortic valve obstruction), hypertension, diabetes mellitus, coronary artery disease, acute mitral regurgitation, or infiltrative disease of the myocardium. An S₃ attributable to right ventricular (RV) hypertrophy may develop with cardiac disease, pulmonary hypertension, or pulmonary valve stenosis. However, an S₃ has been documented with apparently normal ventricular compliance in patients with severe anemia, peripheral atriocventricular fistula, and thyrotoxicosis.

Not everyone agrees that an S₃ in a near-septagenarian is abnormal. LV compliance does diminish with age and may account for an S₃ in its own right without other pathology present. When present in this particular clinical setting, we must acknowledge the likelihood of coronary ischemia. Those who have worked in the catheterization laboratory have probably seen, during a coronary angiogram in a patient with coronary atherosclerosis, the sequence of increased LV end-diastolic pressure followed by symptoms of angina pectoris and the development of an S₃. Prompt administration of sublingual nitroglycerin or nifedipine reverses this sequence with disappearance of the S₃ and angina when the LV end-diastolic pressure becomes lower.

There are no other physical findings to hang our hat on here. Hypertension is absent, and there are no physical findings present to suggest other structural changes in the heart or lungs—not even a soft basosystolic ejection murmur of aortic valve sclerosis commonly found in this age group.

Hospital Course

The initial laboratory studies were uncommonly benign: slight elevation of triglycerides (260), total cholesterol (223), LDL (low-density lipoprotein) level (136), and a not unusually low HDL (high-density lipoprotein) level (35) for a man this age.

A chest radiograph provided no new information, nor did a normal resting ECG resting heart rate, 58 beats per minute).

Correctly, he was admitted to the CCU and treated initially for unstable angina with intravenous heparin, intravenous nitroglycerin, and acetylsalicylic acid. Subsequent CPK levels were normal. CK isoenzymes were not obtained.

Approximately 18 hours after admission, he developed typical (for him) chest tightness, which was treated with increase in the nitroglycerin rate of administration producing relief of symptoms in 10 minutes. No ECG changes during the period of chest pain were observed, but 2 hours later, a heart rate of 48 beats per minute was noted. The significance of this is not clear, because we do not know what his normal resting rate had been during this hospitalization. He did report feeling “dizzy.” Treatment with fluids and a decrease in the nitroglycerin drip rate resolved the problem—presumably meaning his dizzy symptom. But, we are not told to what rate his heart returned. If the bradycardia was a significant change, it was possibly the result of a vasovagal reaction. We are not told the coincident blood pressure or any other symptoms that might have been present, such as nausea or diaphoresis.

We are told that diltiazem was added on the third hospital day, lending further credence to our suspicion that a diagnosis of coronary ischemia was entertained by the attending physicians as well. An echocardiogram apparently was not performed, the findings of which might have proved helpful in the discussion to follow. But, by the fifth day, when his clinical syndrome was deemed stable, a diagnostic procedure was performed. I presume this was a diagnostic cardiac catheterization and coronary angiographic study.

Discussion of Differential Diagnosis

We now have the clinical picture of a patient with a chest pain syndrome quite consistent for the most part with coronary ischemia, but for what reason? Gender, age, family history, and modest elevation of total cholesterol, LDL cholesterol, and low HDL cholesterol levels certainly make coronary atherosclerosis the odds-on favorite. But, remember why we are here. For that reason, a review of other causes of chest pain that might be attributed to a coronary ischemic syndrome is appropriate. For discussion purposes I will categorize these as cardiac, vascular, gastrointestinal, pulmonary, and musculoskeletal. And, I will discuss them in reverse order.

There is little in this clinical picture to incriminate a musculoskeletal diagnosis. This is not just any chest pain syndrome, it is quite reproducible and consistent. Nothing is presented to suggest the likelihood of cervical disk disease, arthritis of the shoulder or spine, costochron-
dritis of the sternoclavicular joints, interscalene or hyperabduction syndrome, or bursitis. But, let me relate two personal experiences I have had with physicians who presented with what one thought was angina pectoris and the other thought was cervical spine disease. The first was a middle-aged endocrinologist who experienced high anterior chest pain and left shoulder pain of quite severe degree that occurred only with exertion and was relieved by rest. When questioned closely, his pain was atypical for angina. His diagnosis turned out to be cervical spine disease. The other, a cardiologist, developed very typical exertional substernal pressure with exertion, which was relieved by rest. His interpretation was cervical spine disease. Of course, he really had coronary artery disease with coronary ischemia, illustrating that a patient’s interpretation (especially if a fellow doctor) of symptoms may lead you astray unless you are a thorough investigator.

The gastrointestinal category embraces such entities as esophageal reflux or spasm (the latter often relieved with nitrates and/or calcium channel blockers), peptic ulcer disease, pancreatitis, and perhaps most troublesome, biliary disease. I consider myself a competent clinician, yet I have mistakenly attributed gallbladder pain to coronary ischemia and visa versa. Because the two pathologies are not infrequent companions, it is not a bad idea to consider them both when evaluating this type of problem. How many times have you seen patients undergo coronary artery bypass surgery only later to turn up with active symptomatic biliary disease?

There is little here to incriminate a pulmonary source. Pleurisy, pneumonia, pneumothorax, tumor, chronic obstructive pulmonary disease, all representative of this category, hardly seem the likely culprit.

What about a vascular disorder? Aortic dissection is a possibility. There are no stigmata of Marfan’s syndrome. However, a silent dissection of the ascending aorta compromising the coronary circulation is certainly possible but seems unlikely given the absence of hypertension and the relatively young age for dissection to occur (more common in persons in their 70s and 80s). Has anyone seen sphyllitic aortitis in years? We have no reason to suspect pulmonary embolism (chronic) or pulmonary hypertension from this clinical picture. But that combination can produce a picture very similar to our patient. I recently saw a woman in her mid-40s with a history of progressive fatigue, exertional chest tightness, palpitations with exertion, but also progressive dyspnea on exertion. All symptoms began a year or more following gallbladder surgery complicated by a postoperative pulmonary embolus. Her problem became severe pulmonary hypertension secondary to recurrent pulmonary emboli. But, clues other than history included obvious evidence on physical examination of pulmonary hypertension, RV enlargement, an RV S, and an ECG with RV hypertrophy. The diagnosis was confirmed by echo/Doppler study.

At this point, left me interject a thought about an echo/Doppler study. I am sure there were cogent reasons for not performing one early on in this patient. I would have done so because I think it might have quickly eliminated some of our speculations.

A coronary ischemic syndrome has been described with diffuse vasculitis including entities such as giant cell arteritis, Wegner’s granulomatosis, polyarteritis no-
Coronary angiograms show that during diastole (top), the left anterior descending coronary artery (LAD) is widely patent with a diameter of 1.3 mm. During systole (bottom), a long segment of the artery is diffusely narrowed with a diameter of 0.7 mm. The findings are diagnostic of a myocardial bridge causing functional stenosis of the LAD.
imal right or left main coronary wall. Coronary artery dissection is not the cause of this man's symptoms.

Myocardial hypertrophy is not identified by the ECG or by any clinical clues to suggest the presence of idiopathic hypertrophic subaortic stenosis, aortic valve stenosis, or hypertension. Any of these, if sufficiently severe, could cause subendocardial ischemia and presumably angina pectoris. An infiltrative myocardial process (sarcoid, amyloid, eosinophilia) is rarely associated with a coronary ischemic syndrome.

That brings me to the last two entities. One of them, I suspect, is the likely culprit. The first embraces the likelihood that coronary atherosclerosis is indeed present and that plaque disruption leading to thrombus formation precipitated an accelerating acute coronary syndrome. Plaque disruption may occur following rupture of coronary vasa vasmorum and subplaque hemorrhage. But recent pathological, angiographic, and angiographic studies have demonstrated other important contributors to plaque disruption. Small atherosclerotic plaques with mild to moderate stenosis are likely to be lipid-rich and soft and, therefore, more prone to rupture. Serial angiograms have shown that lesions associated with unstable angina were likely to be only mildly or moderately stenotic on initial examination. These lesions tend to be small and soft with a high concentration of cholesterol and covered by a fibrous cap. Shear forces within the coronary lumen from intraluminal pressures, twisting and bending the vessel with each heart contraction, may make these plaques prone to disruption at the junction of the fibrous cap and the adjacent normal arterial wall. Macrocyes (foam cells) participate in the development of atherosclerotic plaques by virtue of mobilization and metabolism of lipids and other biochemical reactions within the arterial wall. In unstable angina pectoris, the offending plaque is commonly found to be eccentric and irregular in shape, suggesting disruption. Under these circumstances, thrombus formation is likely. This becomes a dynamic process resulting in thrombosis that may wax and wane spontaneously or, of course, may be resolved by thrombolytic therapy. The disruptions may be small and without symptoms but may lead to progression of atherosclerosis by virtue of organization and regrowth of vascular endothelium as healing takes place. It is very possible that this process was operating in our patient.

The other possibility of a coronary ischemic syndrome is extrinsic compression of a coronary vessel. Such may occur with anomalous origin of the left coronary artery from the right coronary artery, or the right coronary aortic sinus, then coursing between the aorta and pulmonary artery. This anomaly tends to become apparent in young people and is a known cause for MI or sudden death. Except for the age factor, this could be an explanation in our patient.

Compression of a coronary artery has been reported also by such diverse causes as an LV pseudoaneurysm, hypertrophic cardiomyopathy alone or with an apical LV aneurysm, and with the Wolff-Parkinson-White syndrome. The most common compression of a coronary artery occurs with isolated myocardial bridging predominantly of the LAD or its branches, or much less commonly of the left circumflex artery. At autopsy, myocardial bridging reportedly occurs in 1% to 3% of the population usually without functional significance. More commonly, myocardial bridging is seen at angiography with an incidence reported from 0.05% to 16%, the vast majority of which are seen in otherwise normal coronary arteriograms. The dynamics of myocardial bridging have been reported by intracoronary ultrasound and Doppler. If identified, its functional significance may be ascertained by thallium stress testing although the vast majority of patients with myocardial bridges are without symptoms. Coronary atherosclerosis within the myocardial bridge is rarely seen at pathological examination or by angiography. It has been reported in children as young as 1 day to 2 years old, occurring in diverse forms of congenital heart disease causing LV hypertrophy. When coronary atherosclerosis is associated with LV hypertrophy, there tends to be a longer segment involved with more severe compression and more likely to be associated with symptoms.

Myocardial bridges can be associated with a coronary ischemic syndrome, acute MI, and death.

Therapeutic intervention is not commonly required because most myocardial bridges seen on angiography are not associated with symptoms. However, when coronary ischemia is encountered, medical therapy with calcium channel blockers and nitrates is the first line of treatment. Coronary artery bypass and myotomy of the muscle segment have been performed with relief of symptoms.

So what pathology does our patient exhibit? The dilemma must be resolved. I believe it is related either to atherosclerotic plaque disruption with thrombus formation in a 67-year-old man with perhaps mild to moderate coronary atherosclerosis or to a myocardial bridge involving a substantial segment of the LAD. The diagnostic procedure performed on the hospital day 5 was an arteriogram and did confirm the presence of a myocardial bridge compressing a long segment of the LAD. We are told that therapy with a calcium channel blocker relieved his coronary ischemic symptoms and he was discharged without further incident.

Diagnostic Procedure

The diagnostic procedure was cardiac catheterization with coronary angiography. The coronary arteries showed no significant areas of discrete narrowing. However, the LAD exhibited a long segment that developed marked narrowing during systole (Fig 2). The findings were diagnostic of a myocardial bridge causing functional compression of the LAD.

Conclusions

The final diagnosis was ischemic heart disease due to coronary compression by a myocardial bridge.

References


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**KEY WORDS** • Clinicopathological Conference • angina
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