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Clinical problem-solving. Through thick and thin.

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Through Thick and Thin

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A 58-year-old woman was admitted to the hospital because of chest pain. The night before admission, the patient awoke with crushing, nonpleuritic chest pain radiating down her left arm, with associated presyncope and diaphoresis. The pain was like cardiac chest pain that she had experienced previously. She had no dyspnea, fever, chills, or cough. She had long-standing hypertension and diabetes mellitus in association with corticosteroid therapy for idiopathic thrombocytopenic purpura, as well as a family history of premature coronary artery disease. She had had two normal pregnancies and one spontaneous abortion. Five months before this admission, she had been admitted because of chest pain. A diagnosis of acute anterior myocardial infarction was made on the basis of electrocardiographic changes and elevated creatine kinase levels. Cardiac catheterization revealed total occlusion of the proximal left anterior descending artery, which was treated with angioplasty and stent placement. Her hospitalization was complicated by dehiscence of a left groin wound and a urinary tract infection with *Escherichia coli*, and she was confined to bed for 10 weeks.

This history is suggestive of myocardial ischemia. The patient has pain like that associated with a previous infarction, and has recently undergone coronary angioplasty and stent placement. Myocardial infarction or unstable angina from closure at the stent site is a likely possibility, especially because about 30 percent of occluded vessels treated with angioplasty become reoccluded within six months. Dressler's syndrome, or postinfarction pericarditis, can present with this type of chest pain, but the patient's use of corticosteroids and the absence of systemic symptoms make this diagnosis less likely. Aortic dissection can also mimic myocardial infarction and should be considered in a patient with hypertension and vascular disease. Confinement to bed increases the risk of pulmonary embolism, but the patient had no dyspnea or hemoptysis, and her chest pain was not pleuritic. Pneumothorax, pneumonia, and abdominal processes such as pancreatitis and perforating ulcer are not compelling possibilities with this history, but they should be kept in mind. I would focus on physical findings of aortic dissection and pericarditis, because the management of these disorders differs substantially from the management of myocardial infarction. I would also like to see a chest film and an electrocardiogram.

On examination, the patient had a cushingoid appearance; she was not in acute distress. Her blood pressure was 120/70 mm Hg in both arms, her pulse was 80 beats per minute and regular, her respirations were 16 per minute, and her temperature was 36.4°C. She had numerous petechiae in her mouth, a hemorrhagic bulla on her tongue, and bilateral xanthelasma. There was no jugular venous distention or carotid bruit, and the findings were normal on auscultation of the lungs and heart. There were no friction rubs or murmurs of aortic regurgitation. The abdomen was soft and nontender, with no pulsatile mass. There was a well-healed splenectomy scar. There was a stage I sacral decubitus ulcer and a healing left groin wound containing granulation tissue. Numerous ecchymoses were present on all the extremities. The pulses were equal and symmetric in all the extremities. An electrocardiogram, which revealed sinus rhythm and evidence of an old anterior infarction, was unchanged from a previous postinfarction electrocardiogram. A chest film showed clear lungs and no mediastinal widening.

Aortic dissection is less likely but is not ruled out by the normal chest film, symmetric pulses, and absence of aortic regurgitation on physical examination. Although the history is suggestive of recurrent myocardial ischemia, there is no electrocardiographic or laboratory evidence of an unstable coronary syndrome, unless the patient has electrocardiographically silent ischemia. My index of suspicion for ischemia remains high, although I have not thoroughly investigated other items on my original differential diagnosis. I would begin treatment with a beta-blocker, but I would not give her aspirin or heparin, since she has idiopathic thrombocytopenic purpura and overt bleeding.

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Values for cardiac enzymes, electrolytes, renal function, liver function, prothrombin time, and activated partial-thromboplastin time were normal. The white-cell count was 7900 per cubic millimeter, the hematocrit was 33.7 percent, and the platelet count was 24,000 per cubic millimeter (base-line value, 60,000 per cubic millimeter during treatment with 4 mg of dexamethasone per day). Arterial-blood gas values while the patient was receiving 4 liters of oxygen per minute were as follows: pH, 7.50; partial pressure of carbon dioxide, 38 mm Hg; and partial pressure of oxygen, 89 mm Hg.

The elevated alveolar–arterial gradient increases the likelihood of pulmonary embolism, even in the absence of pleuritic chest pain, dyspnea, and tachycardia. I would obtain a lung scan immediately. Because the patient has active bleeding and thrombocytopenia, I would not treat her with anticoagulants until I was convinced that she had pulmonary embolism.

Ventilation–perfusion scanning showed a single large perfusion defect in the left upper lobe without a matching ventilation defect. The finding was interpreted as indicating an "intermediate probability" of pulmonary embolism. Duplex ultrasonography of the lower extremities was normal. Intravenous heparin treatment was started. The patient's platelet count, obtained six hours later, was 4000 per cubic millimeter, and the patient had epistaxis and worsening ecchymoses on her extremities. Urine culture and two sets of blood cultures were all positive for *E. coli*, and intravenous antibiotics were administered.

Her infection has probably worsened the thrombocytopenia and triggered bleeding, and now there is a risk of a catastrophic hemorrhage. Because of the high risk of bleeding, I would worry considerably about giving her heparin. Lung scans indicating an intermediate probability of embolism have a moderate false positive rate, and in view of the normal findings on leg ultrasonography, I believe it is essential to obtain a pulmonary angiogram. We should not forget that thrombi can form despite severe thrombocytopenia. I would also treat her with intravenous immune globulin for the thrombocytopenia.

Pulmonary angiography was performed without complications, and a clot in the anterior segment of the left upper lobe was found. Other laboratory results obtained before initiating therapy with heparin included a dilute-Russell's-viper-venom time of 37.3 seconds (normal range, 21.4 to 36.2) and a positive test for IgG anticardiolipin antibody. The results of tests for protein C, protein S, and antithrombin III were normal; a test for antibody to the human immunodeficiency virus and a polymerase-chain-reaction assay for the factor V Leiden mutation were negative. A review of her medical records from another hospital did, however, reveal a history of deep venous thrombosis the previous year. Treatment with warfarin resulted in anticoagulation without further bleeding, and heparin was discontinued. Several days after the initiation of treatment with intravenous immune globulin and antibiotics, her platelet count increased to more than 200,000 per cubic millimeter, and she had no clinically evident episodes of bleeding or clotting.

COMMENTARY

Pulmonary thromboembolism accounts for up to 250,000 hospitalizations and 50,000 deaths each year in the United States.[1] Only one third of emboli confirmed at autopsy are diagnosed before death,[2,3] reflecting the difficulty of establishing the diagnosis. Since the 1960s, there has been no significant reduction in mortality from pulmonary embolism,[4] despite the widespread use of lung scanning and angiography.[5,6] The experience with this patient underscores the importance of a high index of clinical suspicion and a rational approach to testing.

The patient presented with chest pain that was like the pain associated with a previous myocardial infarction in the context of confinement to bed and active idiopathic thrombocytopenic purpura. The index of suspicion for recurrent myocardial ischemia was high because 30 percent of occluded coronary vessels become reoccluded within six months after angioplasty.[7] Even so, the discussant thoughtfully formulated a differential diagnosis that included vascular, pericardial, pulmonary, and gastrointestinal processes. The initial evaluation focused on signs of aortic dissection and pericarditis, since the usual approaches to the treatment of myocardial infarction — anticoagulation, thrombolysis, or angioplasty — would be hazardous in the presence of these disorders. However, the discussant found no evidence of an unstable coronary syndrome, aortic dissection, pneumothorax, or pneumonia.

It is critical to have a high index of suspicion for pulmonary emboli in a patient with unexplained recent chest pain, dyspnea, or tachypnea. Palla and colleagues[8] showed that the presence of any one of these symptoms, without an obvious explanation indicated by the findings on a routine chest film and electrocardiogram, has a sensitivity of 97 percent and a specificity of 24 percent for detecting pulmonary embolism. This initial emphasis on diagnostic sensitivity minimizes the possibility of a missed diagnosis, since clinical criteria alone are notoriously unreliable in establishing the diagnosis. Indeed, the patient had none of the findings known to be spe-

cific for pulmonary emboli, such as pleuritic chest pain,[9] sudden dyspnea,[9] tachypnea,[10,11] hemoptysis,[12] and jugular-vein distention.[9] Instead, less specific features were present, including a history of confinement to bed (reported in 55 percent of patients with pulmonary embolism), nonpleuritic chest pain (reported in 14 percent), and diaphoresis (reported in 27 percent).[12] The chest film, which is abnormal in more than 80 percent of patients,[9] was normal in our patient. The most common electrocardiographic abnormalities in patients with pulmonary embolism, sinus tachycardia (in 44 percent of patients)[9] and nonspecific ST depression (in 50 percent), were both absent in our patient. By maintaining a high clinical index of suspicion for pulmonary embolism, with an initial emphasis on diagnostic sensitivity, the discussant considered the correct diagnosis from the start.

A definitive diagnosis of pulmonary embolism was established through standard radiologic evaluation.[13,14] Ventilation–perfusion scanning, the initial step, was interpreted as indicating an intermediate probability of embolism, but because approximately 30 percent of patients with this kind of result have pulmonary emboli,[5] venous ultrasonography was performed and revealed no thrombus. Hull and colleagues[6] reported that ambulatory, clinically stable patients with suspected pulmonary embolism and nondiagnostic lung scans do well without anticoagulation therapy if serial, noninvasive leg tests are negative. However, because the patient had another predisposing factor (confinement to bed), a pulmonary angiogram, the reference standard, was obtained, and a thrombus was documented.

Was it inappropriate to expose a patient with active bleeding to the dangers of angiography? A previous Clinical Problem-Solving article[15] examined the potential harm of invasive procedures and the risks of empirical treatment in the face of diagnostic uncertainty. The particular case involved a patient with typical features of the hypereosinophilic syndrome, at least in retrospect. Numerous invasive tests were performed to rule out cancer before corticosteroid therapy was initiated. The authors concluded that the diagnostic certainty was reasonably high and the risk of empirical therapy was not considerably greater than that of further evaluation. In our patient, however, the diagnostic certainty was low, because the combination of severe thrombocytopenia, active bleeding, an equivocal lung scan, and a negative leg ultrasound study did not support the diagnosis of pulmonary embolism. Although thrombi can form without platelets,[16] the discussant believed that empirical anticoagulation therapy posed an unacceptable risk of catastrophic hemorrhage.[9] Hence, the one-time risk of angiography, although nontrivial, was justifiable, because it provided a definitive and timely diagnosis in this hemostatic predicament. In the future, noninvasive imaging methods such as spiral computed tomography[17] and magnetic resonance angiography[18] may be useful in these types of cases, but this clinical situation merited the diagnostic gold standard.

Once angiography confirmed the presence of a thrombus, the next decision was whether to treat the patient with anticoagulants or place an inferior vena cava filter. At first glance, the patient's active idiopathic thrombocytopenic purpura and concomitant pulmonary embolism appeared to be clear indications for the placement of a filter. Inferior vena cava filters, which help prevent pulmonary embolization of thrombi distal to the inferior vena cava, are often used in patients with overt bleeding from anticoagulants, those likely to have bleeding with anticoagulants, and those in whom anticoagulation fails; such filters are also used for prophylaxis against thromboembolism in patients with limited cardiopulmonary reserve.[13,19] Although these devices are used frequently, there are few studies of their efficacy and safety. In a recent randomized clinical trial,[20] the presence of filters in patients with deep venous thrombosis reduced the rate of pulmonary embolism in the first 12 days of treatment but did not affect the mortality rate at 2 years. Moreover, filters were associated with an excessive rate of deep venous thrombosis. Temporary, removable filters are still under investigation and may eventually offer attractive alternatives in patients such as ours, because they may provide the short-term benefit of caval interruption without the long-term risks demonstrated by this trial.

The patient was treated with intravenous unfractionated heparin, which is standard therapy for acute venous thromboembolism in North America. This practice may soon change, because two recent clinical trials[21,22] and a meta-analysis[23] concluded that subcutaneous low-molecular-weight heparins were at least as safe and effective as intravenous unfractionated heparin in the treatment of acute venous thromboembolism. Low-molecular-weight heparins also produce more predictable anticoagulation[24] and are less likely to cause thrombocytopenia,[25] both of which were considerations in this patient. Immediately after the initiation of treatment with unfractionated heparin, the patient's thrombocytopenia worsened, probably because of worsening urosepsis and idiopathic thrombocytopenic purpura, not heparin-induced thrombocytopenia, which typically develops five or more days after treatment is initiated.[25] Even if the patient had had true heparin-induced thrombocytopenia, low-molecular-weight heparin would have been contraindicated because of cross-reactivity between the two forms.[26] Thus, the heparin therapy was continued to treat the venous thromboembolism; intravenous immune globulin and antibiotics were administered to combat the idiopathic throm-

bocytopenic purpura and urosepsis, the two main causes of the thrombocytopenia.

The final variable that affected this patient's treatment was documentation of the antiphospholipid syndrome. Multiple thromboembolic events in a patient with idiopathic thrombocytopenic purpura prompted an evaluation for thrombophilia, the formation of recurrent thrombi. Congenital deficiencies of protein C, protein S, and antithrombin III, as well as the presence of the factor V Leiden mutation, have been associated with thrombophilia, but these abnormalities were not present in our patient. Her pregnancy history, however, was consistent with the presence of the antiphospholipid syndrome, and the elevated anticardiolipin-antibody titer and prolonged dilute-Russell's-viper-venom time confirmed the diagnosis.[27] Both recurrent arterial thrombosis[28] and recurrent venous thrombosis[29] are associated with the antiphospholipid syndrome, even in the presence of severe thrombocytopenia.[16] Thus, the patient's major risk factors for thrombosis appear to have been the antiphospholipid syndrome and confinement to bed. Thrombosis in such patients is best prevented with warfarin therapy, with the international normalized ratio at or above 3,[28] which was the treatment used in this case.

Like many cases, this one hardly fit the neat algorithms delineated in textbooks and clinical practice guidelines. What lessons can we learn from this case? First, chest pain in a patient with pulmonary embolism can have an unusual presentation, so unexplained chest pain merits at least a consideration of the possibility of thromboembolism. Second, pulmonary angiography may be necessary to confirm the diagnosis. In this patient, the results were invaluable in justifying the risk of anticoagulation therapy. Third, sepsis causes thrombocytopenia. Fourth, multiple risk factors often contribute to the development of venous thromboembolism. Finally, better therapies are needed in the treatment of venous thromboembolism in patients at high risk for bleeding. Despite the multiple causes and consequences of hemostatic compromise, an appropriate diagnostic approach coupled with careful clinical judgment allowed the discussant to maneuver through thick and thin in addressing our patient's clotting and bleeding.

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