61-Year-Old Woman With Systemic Lupus Erythematosus and Chest Pain

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A 61-year-old woman with history of systemic lupus erythematosus (SLE) and secondary antiphospholipid syndrome (APS) (antinuclear antibodies, 6.4 U [reference range, ≤1.0 U], anti–double-stranded DNA IgG antibodies, 99.9 IU/mL [reference range, <30 IU/mL], IgG β2-glycoprotein 1 antibody, 68 U/mL [reference range, <10.0 U/mL]) was transferred to our hospital for management of acute pleuritic chest pain, scant hemoptysis, and hypoxic respiratory distress. Her SLE manifestations previously included aphthous stomatitis, arthritis, photosensitivity, and malar rash, which were quiescent with hydroxychloroquine treatment. Her medical history was complicated by recurrent venous thromboembolism and stroke requiring chronic anticoagulation using warfarin, with a target international normalized ratio (INR) of 2.5 to 3.5. On arrival at our hospital, the patient was afebrile (temperature, 36.8°C) but hypotensive (blood pressure, 86/62 mm Hg) and hypoxemic (oxygen saturation while breathing room air, 84%), requiring transient vasopressor and noninvasive ventilatory pressure support with 60% fraction of inspired oxygen. Chest pain resolved soon after initiation of bilevel positive airway pressure assistance. Physical examination findings were notable for bilateral lower lung field inspiratory crackles, soft systolic murmur with radiation to the axilla, and nondistended jugular venous pulse. Unilateral right lower extremity swelling was present, and an acute deep venous thrombosis was confirmed on bedside ultrasonography, prompting immediate heparin infusion.

Laboratory values (reference ranges provided parenthetically) revealed therapeutic anticoagulation (INR, 3.3; factor II, 13% [75%-145%]; factor X, 6% [70%-150%]), normocytic anemia (hemoglobin, 9.2 g/dL [12.0-15.5 g/dL]), normal white blood cell count (7.7×10^9/L [$3.5\text{-}10.5 \times 10^9$/L]), modestly increased C-reactive protein (13 mg/L [≤8.0 mg/L]), and a substantially elevated troponin T level (1.8 ng/mL [<0.01 ng/mL]). Arterial blood gas measurement while the patient received 60% fraction of inspired oxygen revealed a pH of 7.23 (7.35-7.45), PCO_2 of 55 mm Hg (35-45 mm Hg), and HCO_3^- of 22 mmol/L (22-29 mmol/L), consistent with acute respiratory acidosis. Electrocardiography (ECG) revealed 0.5-mm ST-segment depressions in leads V_4 through V_6. Portable chest radiography (CXR) identified diffuse patchy airspace opacities throughout both lungs with more confluent areas of consolidation in the retrocardiac left lung base. Initial transthoracic echocardiography (TTE) revealed a left ventricular ejection fraction of 59% and normal regional wall motion.

1. Which *one* of the following is the *most likely* cause of this patient's pleuritic chest pain?

a. Acute coronary syndrome (ACS)
b. Myocarditis
c. Pulmonary embolism
d. Pneumonia
e. Diffuse alveolar hemorrhage (DAH)

The diagnosis of pleuritic chest pain in a patient with SLE and APS is challenging. Systemic lupus erythematosus is an autoimmune condition with widespread organ involvement including coronary and noncoronary cardiac manifestations.[1] Chest pain and troponin T elevation raise concern for ACS, particularly with ST changes on ECG. However, ACS alone would not explain the presenting features of hypoxemia, diffuse lung opacities, and scant hemoptysis in the setting of normal TTE findings. It is possible that the patient has concurrent non–ST elevation myocardial infarction or type 2 demand ischemia from worsening anemia and hemodynamic instability. This diagnosis should be further evaluated by trending troponin and possible coronary

See end of article for correct answers to questions.

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angiography following hemodynamic stabilization. Chest pain and "troponinemia" can also be seen in myocarditis, although more diffuse ST elevation on ECG and abnormalities on echocardiography would be expected. The presence of acute anemia, hemoptysis, and diffuse lung opacities is more suggestive of a primary pulmonary process. Antiphospholipid syndrome, a prothrombotic condition affecting both venous and arterial vessels, can increase the risk for pulmonary embolism and DAH.[2] The absence of the Westermark sign on CXR and the lack of right ventricular strain on TTE in combination with the supratherapeutic INR level make pulmonary embolism unlikely. Severe pneumonia complicated by sepsis could account for the hypotension, hypoxia, and scant hemoptysis; however, leukocytosis and fever would be anticipated. It is reasonable, however, to administer antibiotics empirically for pneumonia. In the setting of a known chronic autoimmune condition, anemia, hemoptysis, and diffuse patchy opacities on CXR, the suspicion for DAH causing pleuritic chest pain is high and should be further evaluated.[3]

High-resolution noncontrast chest computed tomography revealed diffuse ground-glass opacities. Broad-spectrum intravenous antibiotics were initiated empirically for possible pneumonia. The patient's respiratory status precipitously declined, requiring immediate intubation and transfer to the intensive care unit.

2. Which *one* of the following is the *most appropriate* next step to confirm the cause of hemoptysis?

a. Blind protected bronchoalveolar lavage (BAL)
b. Fiberoptic bronchoscopy with BAL
c. Transesophageal echocardiography
d. Coronary angiography
e. Cardiac magnetic resonance imaging (MRI)

A blind protected (double-lumen catheter) BAL can identify a bloody tracheal aspirate but does not disclose the location of the bleeding. The criterion standard for diagnosing DAH is flexible fiberoptic bronchoscopy with sequential BAL.[4] Sequential BAL is performed by instilling and retrieving 3 aliquots of 50- to 60-mL sterile nonbacteriostatic saline from a subsegmental bronchus. Alveolar hemorrhage is confirmed when lavage aliquots become progressively more hemorrhagic, a finding that differentiates DAH from other causes of hemoptysis. Hemosiderin-laden macrophages found in BAL fluid, which are visualized by Prussian blue staining, can also be used to diagnose DAH, especially when more than 20% of 200 macrophages stain positive.[5] This finding is especially helpful in diagnosing DAH in the absence of frank hemoptysis or a grossly hemorrhagic BAL. Transesophageal echocardiography provides superior detail compared with TTE for heart valves and the atrial septa but has a limited role in evaluating hemoptysis. Coronary angiography and cardiac MRI would rule out the presence of coronary obstruction and myopericardial inflammation, respectively, but would not be helpful in confirming DAH.

Fiberoptic bronchoscopy with sequential BAL produced progressively bloody return with 30% hemosiderin-laden macrophages, supporting the diagnosis of DAH.

3. Which *one* of the following is the *most appropriate* next step in the management of this patient's hemoptysis?

a. Discontinue heparin
b. Discontinue heparin and administer protamine sulfate
c. Discontinue heparin, administer protamine sulfate, and transfuse fresh frozen plasma
d. Interventional radiology–guided catheter embolization
e. Trial of pulse-dose methylprednisolone

The presence of deep venous thrombosis in the setting of therapeutic anticoagulation is more suggestive of an underlying vascular microthrombotic event and capillaritis underlying the bleeding diathesis. Discontinuing antithrombotic agents such as heparin or reversing anticoagulation using protamine sulfate or fresh frozen plasma are not indicated because that would increase the risk for further thrombotic events and conversion to a catastrophic antiphospholipid antibody syndrome, which has a high mortality rate. Pulmonary coil embolization has been used to treat arteriovenous malformations but has no role in management of DAH because most of the bleeding is mediated by a

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microthrombotic process and is often localized to the level of the alveolar septae and pulmonary capillaries, which are not amenable to such a procedure. Most diseases causing capillaritis are treated with a combination of systemic glucocorticoids and immunosuppressive therapy, such as cyclophosphamide or rituximab. Often, pulse-dose glucocorticoids are initiated while awaiting the results of testing to confirm a specific cause of capillaritis, which will then guide selection of additional immunosuppressive therapy. Most experts recommend administering intravenous pulse methylprednisolone (500-1000 mg in divided doses daily) for up to 5 days followed by transition to high-dose oral glucocorticoids with a gradual taper and initiation of a corticosteroid-sparing agent for maintenance therapy. In addition to corticosteroids, anticoagulation should also be continued when possible. The preferred anticoagulation in this setting is unfractionated heparin because it can be reversed quickly if necessary.

Heparin infusion was continued, and pulse-dose glucocorticoids were initiated with 1000 mg of intravenous methylprednisolone daily. Despite radiographic resolution of DAH within 24 hours and symptomatic improvement in oxygenation, the troponin T level remained elevated (1.3 ng/mL) and chest pain recurred. Repeated troponin T measurements at 3 and 6 hours were 1.5 ng/mL and 1.7 ng/mL, respectively. Electrocardiography documented normal sinus rhythm with persistent ST depressions in the anterolateral leads. A second TTE disclosed a 15% decrease in left ventricular ejection fraction and development of regional wall motion abnormalities, more pronounced in the anterior and apical regions. In the interim, moderate mitral and tricuspid valve regurgitations had also developed.

4. Which *one* of the following is the *most likely* cause of this patient's recurrent chest pain?

a. Myocarditis
b. Endocarditis
c. Pericarditis
d. Coronary arteritis
e. ACS

Myocarditis, endocarditis, and pericarditis are common cardiac manifestations of SLE, with a reported prevalence of 3% to 15%, 32% to 38%, and 11% to 54%, respectively.[1] Myocarditis is often characterized by the presence of diffuse T-wave inversion or saddle-shaped ST-segment elevation on ECG, which is not present in this case. Cardiac MRI can be used to help diagnose myocarditis, but tissue biopsy is considered the diagnostic standard. Endocarditis often presents with new mitral regurgitation or nonbacterial valvular vegetations manifesting as valvular dysfunction or embolic phenomenon. Systemic lupus erythematosus—associated pericarditis often manifests as diffuse ST-segment elevation on ECG and as pericardial rubs on cardiac auscultation. In the absence of characteristic ECG, TTE, and physical examination findings, myocarditis, endocarditis, and pericarditis are unlikely causes of the patient's recurrent chest pain.

Coronary arteritis is a rare manifestation of SLE with unknown prevalence. It can be diagnosed by coronary angiographic evidence of a characteristic coronary saccular aneurysm in the absence of an obstructing lesion or acute development of an obstructive lesion in previously normal coronary arteries.[6] Coronary arteritis is unlikely in this patient but should be considered.

Patients with SLE have an accelerated rate of atherosclerosis, with ACS often developing even in the absence of conventional cardiovascular risk factors.[7,8] In this patient, the presence of recurrent chest pain, increasing troponinemia with notable delta wave, and ST-segment depression on ECG with evolving regional wall motion abnormalities supports the diagnosis of ACS.

Coronary angiography identified severe multivessel coronary atherosclerosis, including 90% stenosis of the proximal left main coronary artery, 90% stenosis of the proximal left anterior descending artery, 90% obstruction of the proximal circumflex artery, and 80% obstruction of the distal right coronary artery. An intra-aortic balloon pump was inserted, and the patient was transferred to the cardiac intensive care unit.

5. Given the findings and the patient's comorbidities, which *one* of the following is the *most appropriate* intervention?

a. Coronary artery bypass graft surgery
b. Percutaneous coronary intervention with stent placement

c. Referral for left ventricular assist device
d. Referral for heart transplant
e. Medical management

Current American College of Cardiology/American Heart Association guidelines highlight the benefit of coronary artery bypass graft surgery over percutaneous coronary intervention for the management of left main or multivessel coronary artery disease. In the setting of SLE and APS, the management of left main or multivessel disease is complex. Limited studies have found high intraoperative mortality (89%) and postoperative complications (84.2%) associated with cardiac surgery in patients with APS.[9,10] Because of the high rate of morbidity and mortality associated with intracardiac surgery, complex percutaneous coronary intervention is reasonable in such cases. However, there is a higher risk for repeated target vessel revascularization after 6 months in patients who have APS compared with patients who have ST-elevation myocardial infarctions without APS.[11] At the present time, our patient would not meet criteria for either left ventricular assist device or cardiac transplant. Medical management, although reasonable in patients with multiple comorbidities, would be difficult in this situation in which the guideline-driven use of medications would be limited by the patient's tenuous hemodynamics.

The patient underwent complex angioplasty with placement of 5 drug-eluting stents in the affected coronary lesions, which led to hemodynamic stability and immediate resolution of her chest pain. She was discharged from the hospital 72 hours later in good condition with a treatment regimen of warfarin and clopidogrel.

DISCUSSION

Chest pain is a common clinical presentation in both the inpatient and outpatient settings. The differential diagnosis for patients presenting with chest pain is broad, ranging from benign disorders such as musculoskeletal chest pain to life-threatening myocardial infarction or pulmonary embolism. In patients with autoimmune disease, such as SLE or APS, the cause of chest pain can be difficult to ascertain because of atypical clinical presentation, antibody-mediated laboratory abnormalities, and physician unfamiliarity with this population. In general, chest pain in patients with underlying autoimmune conditions requires a thorough work-up because of the increased risk of life-threatening complications associated with the inflammatory and/or prothrombotic state. This case illustrates the challenge associated with the diagnosis and management of chest pain in a patient with SLE and/or APS, particularly in the setting of hypoxic respiratory failure and hemodynamic instability.

Systemic lupus erythematosus is an autoimmune condition with heterogeneous clinical presentation and the presence of one or more antinuclear, anti—double-stranded DNA, or anti-Sm antibodies. Systemic lupus erythematosus has a reported prevalence of 25 to 150 cases per 100,000 population. This condition has widespread organ involvement. Cardiac manifestations are also common and can include inflammation of the pericardial, myocardial, and endocardial layers as well as accelerated coronary atherosclerosis formation in the absence of normal risk factors. Systemic lupus erythematosus is associated with a higher risk of APS than found in the general population. Among patients with SLE, the prevalence of antiphospholipid antibodies ranges from 15% to 34% compared with 1% to 5% in the general population. Antiphospholipid syndrome may develop in 50% to 70% of patients with SLE who harbor antiphospholipid antibodies after 20 years of follow-up.[12] Patients with APS generate antiphospholipid antibodies that bind to various plasma proteins involved in the anticoagulation pathway, such as protein C, protein S, or thrombomodulin. This process results in an increased risk of thrombi formation in the arterial and venous vessels throughout the body. When the pulmonary vasculature is involved, chest pain accompanied by a bleeding diathesis called DAH can occur. The criterion standard for diagnosing DAH is through fiberoptic bronchoscopy and bloody return on sequential BAL. The presence of at least 20% of 200 macrophages stained positive for hemosiderin can also be used to diagnose DAH in the absence of frank bloody return.

The pathophysiology of DAH in the setting of APS is not completely understood.

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The most commonly described manifestation of DAH is vascular thrombosis, with resulting end-organ injury mediated by APS-induced activation of endothelial cells and platelets with resultant complement activation and inhibition of anticoagulant factors.[4] Capillaritis has also been implicated in DAH. This process is mediated by APS-induced up-regulation of endothelial cell adhesion molecules with subsequent neutrophil recruitment and migration into the alveolar septae resulting in tissue destruction and hemorrhage.[13] Patients with APS who have DAH benefit from systemic glucocorticoids and/or immunosuppressive therapy, such as cyclophosphamide or rituximab. Unlike other etiologies of DAH, APS-mediated DAH requires continuation of anticoagulation despite an active bleeding process. The rationale behind this requirement is that the bleeding cascade was initiated by a thrombotic event and discontinuation will result in the propagation of existing thrombi and generation of new thrombus.

Coronary artery disease is common in patients with SLE and has considerable impact on morbidity and mortality. According to the Framingham Offspring Study, women in the 35- to 44-year age group who have lupus are more than 50 times more likely to have a myocardial infarction compared with women of similar age without lupus.[14] In addition, a recent prospective cohort study evaluating atherosclerotic events in patients with SLE found that 1.8% of the participants were affected within 2 years of study enrollment.[15] Given the high risk of accelerated atherosclerosis, even in the absence of traditional cardiovascular risk factors, coronary angiography in the setting of ECG changes or cardiac enzyme elevation is warranted. The management of coronary artery disease in the setting of SLE and APS with multivessel involvement continues to be controversial. Small case series and retrospective studies have suggested increased perioperative or postoperative complications associated with cardiothoracic procedures, including coronary artery bypass graft surgery.[10] At this time, only limited observational data is available documenting the safety and efficacy of percutaneous coronary intervention with drug-eluting stent placement in this population, and further research is needed. Furthermore, insufficient evidence is available to guide postintervention anticoagulation. For patients who continue to take warfarin, monitoring factor Xa levels is suggested to assess adequate anticoagulation because the INR can be unreliable in these patients. Antiplatelet regimens are recommended after stent placement, and the use of both aspirin and clopidogrel has been suggested. This combination, however, is associated with an increased risk of bleeding complications, particularly in patients receiving glucocorticoids. If a single antiplatelet agent is added to warfarin, clopidogrel is preferred by some experts, as was done in our patient. We recommend collaboration among the patient/family, primary medicine team, and consulting services (cardiology, cardiothoracic surgery, rheumatology) to discuss individualized treatment options in these complex cases.

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CORRECT ANSWERS: 1. e. 2. b. 3. e. 4. e. 5. b.

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