A 39-year-old man with sudden onset of chest pain

A 39-YEAR-OLD MAN with a history of a transient ischemic attack and poorly controlled hypertension presents to a community hospital with the sudden onset of substernal chest pressure radiating to both arms. The pressure is somewhat relieved by sitting. He also has bilateral muscle spasms in the lateral aspect of his chest wall that worsen with deep breathing.

For the past 2 years, he has had gastroesophageal reflux disease, dyslipidemia, occasional low-grade fevers, and dryness on his nose and cheeks. He denies having shortness of breath, joint pain, cough, or recent viral illness. He takes no medications and says he does not smoke or use illegal drugs.

The patient’s mother has hypertension and diabetes mellitus and has had a myocardial infarction. His brother has autoimmune hepatitis.

His physical examination is remarkable only for tachypnea and tachycardia.

Electrocardiography (ECG) is performed and shows lateral ST-segment elevation, particularly in leads I, V5, and V6; inferior ST-segment elevation with downward concavity, and PR-segment elevation in lead aVR.

The patient is given morphine and nitroglycerin, but he continues to have chest pain. He is transferred to a larger medical center for further tests and care.

Cardiac catheterization shows normal coronary arteries without evidence of obstruction. The left ventricular ejection fraction is 60%.

Echocardiography shows a thin echo-free space between the myocardium and the pericardium, suggestive of pericardial fluid.

On physical examination, a pleuropericardial rub is now noted. The patient is diagnosed with pericarditis on the basis of the history, physical examination, ECG, and echocardiography.

DETERMINING THE CAUSE OF PERICARDITIS

The patient is admitted to the hospital for treatment and to investigate the cause of pericarditis.

Laboratory values, diagnostic tests

- Platelet count 90,000/mm³ (normal 150,000–450,000)
- Absolute lymphocyte count 1,846/mm³ (normal 1,500–4,500)
- Erythrocyte sedimentation rate 92 mm/hour (normal 0–15)
- Creatinine concentration 1.4 mg/dL (normal 0.7–1.4)
- Antinuclear antibody (ANA) test: positive, speckled pattern, titer 1:640
- Human immunodeficiency virus negative

Urinalysis. Protein 30 mg/dL, 5–10 red blood cells per high-powered field.

Chest radiography. Increased cardiac silhouette, bibasilar atelectasis.

Ventilation-perfusion scan. Low probability for pulmonary embolism.

Rheumatology consult. Anti-Smith and antiribonucleic protein antibody assays are positive, complement levels are normal, and anti-dsDNA antibody assays are negative.

The patient is diagnosed with pleuropericarditis due to systemic lupus erythematosus (SLE) on the basis of several criteria: positive ANA, positive anti-Smith and antiribonucleic protein tests, serositis, and thrombocytope-
nia. He is started on prednisone for SLE-related pericarditis and hydroxychloroquine (400 mg/day) for the SLE itself.

**CRITERIA FOR SLE ARE NOT HARD-AND-FAST**

SLE, one of the more common autoimmune diseases, disproportionately affects African Americans and women of childbearing age. It is a noninfectious inflammatory process with serious cardiovascular complications, and it also involves the brain, skin, joints, kidneys, and serous membranes.

“Classification” criteria for SLE, revised by Tan et al in 1982 and by Hochberg in 1997, require at least 4 of the following 11 features:

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis
- Serositis
- Renal disease—proteinuria (> 0.5 g/day or dipstick 3+) or cellular casts
- Neurologic disease—seizures or psychosis
- Hematologic disorders—hemolytic anemia or leukopenia (< 4000/mL) or lymphopenia (< 1500/mL) or thrombocytopenia (< 100,000/mL)
- Immunologic abnormalities (any of the following): anti-dsDNA antibodies; anti-Smith antibodies; a positive finding of antiphospholipid antibodies based on an abnormal serum concentration of immunoglobulin (Ig)G or IgM antiphospholipid antibodies; a positive test result for lupus anticoagulant; or a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization
- Positive antinuclear antibody test.

These criteria were initially developed as inclusion criteria for research studies but have since become de facto diagnostic criteria, offering a methodologic approach for evaluating patients. Patients need not meet the criteria to receive a diagnosis of SLE. The criteria should merely serve as a tool for internists and other nonrheumatologists: seeing some of the criteria in a patient should trigger suspicion of SLE and help direct the diagnostic workup and treatment.

About 25% of patients with SLE have clinical cardiac involvement, which may include pericardial disease, myocarditis, valvular heart disease, endocarditis, conduction abnormalities, and premature or accelerated coronary artery disease.

**FEATURES OF PERICARDITIS**

1. Which of the following is true of acute pericarditis?
   - It is an uncommon manifestation of SLE
   - It can only be diagnosed by echocardiography
   - Classic changes on ECG include diffuse ST-segment elevation, PR-segment depression, T-wave inversion, and PR-segment elevation in lead aVR
   - Therapy is primarily with pericardiocentesis

   The classic changes on ECG are as stated above; the other answers are false.

   Pericardial involvement is the most common cardiac abnormality of SLE. The reported prevalence of pericarditis in patients with SLE ranges from 12% to 48%. Pericarditis is often seen with pleurisy or pleural effusions. Estes and Christian found that 76% of patients with SLE had concomitant pleuritis.

   Acute pericarditis is the initial manifestation of SLE in about 5% of patients, and clinical pericarditis is evident in about 25%. Asymptomatic pericardial effusions are more common than clinical pericarditis: about 42% of patients with SLE have echocardiographic evidence of pericardial effusions, and autopsy studies have shown pericardial involvement in 47% to 83%. For most patients with SLE, pericardial involvement is benign, and tamponade is rare.

   Pericarditis in SLE has the same clinical signs and symptoms as pericarditis in general. Patients may have positional precordial or substernal chest pain associated with fever, tachycardia, and muffled heart sounds. The jugular venous pressure may be elevated, and, especially if cardiac tamponade is imminent, there may be pulsus paradoxus (a decline of more than 10 mm Hg in systolic blood pres-
sure during inspiration).

As mentioned, ECG may show the classic changes of pericarditis: diffuse ST-segment elevation, PR-segment depression, T-wave inversion, and PR-segment elevation in lead aVR. Electrical alternans might also be present with a large pericardial effusion.

Chest radiography may show an enlarged cardiac silhouette or, if the effusion is large, a water-bottle-shaped heart.

Transthoracic echocardiography can ascertain the presence and size of a pericardial effusion, but a large pericardial effusion is not necessary for the diagnosis of pericarditis.

Pericardial fluid analysis is not necessary to make the diagnosis, but it may reveal an exudative effusion with leukocytosis (mostly polymorphonuclear leukocytes), an elevated protein content, and a normal or low glucose concentration. Complement levels may be low. Lupus erythematosus cells and autoantibodies such as ANA and anti-dsDNA may be present.

Echocardiography may show adhesions or fibrinous deposits in the pericardium. Constrictive pericarditis is rare but pericardial thickening may be present.

Acute therapy for pericarditis includes nonsteroidal anti-inflammatory drugs and glucocorticoids. The underlying disease should be controlled; in this case, SLE should be treated with a drug such as hydroxychloroquine.

Pericardiocentesis may be required if an effusion is causing hemodynamic instability.

■ MYOCARDIAL INVOLVEMENT

2 How many of the following statements are true regarding myocardial disease in SLE?

- It can be diagnosed by history and physical examination alone

- Steroids are the primary treatment for SLE-related myocarditis

- Hydroxychloroquine is rarely associated with cardiomyopathy

- Only diastolic dysfunction is seen in patients with SLE

The first three answers above are true.

Myocarditis in SLE is not as common as pericarditis: it is clinically apparent in 10% to 14% of patients with SLE but is evident on autopsy in 40% to 50%.

■ VALVULAR HEART DISEASE AND ENDOCARDITIS

3 Which of the following is true about Libman-Sacks endocarditis?

- It is another term for subacute bacterial endocarditis

- It cannot always be demonstrated by transthoracic echocardiography

- It only affects the tricuspid valve

- It does not cause significant valvular dysfunction

Diagnosis. Clinical features of myocarditis associated with SLE are similar to those of myocarditis in general and include chest pain, dyspnea, and tachycardia, with signs of congestive heart failure in patients with progressive disease. The diagnosis should not be made by history and physical alone.

Although myocarditis has no specific histopathologic features, endomyocardial biopsy in patients with SLE may reveal immune complex deposition, patchy fibrosis, myocyte necrosis, and perivascular lymphocytic infiltration, however, complement deposits can be found in the myocardium even if an inflammatory cell infiltrate is absent, making the value of biopsy for definitively diagnosing myocarditis unclear.

Echocardiography can be valuable in defining the extent of involvement and to assess the degree of left ventricular dysfunction with active myocarditis. Indium-111-antimyosin Fab imaging studies have also been used experimentally.

Treatment of SLE-related myocarditis is primarily with steroids. Additional immunosuppressive agents have proven helpful for patients with active disease demonstrated by endomyocardial biopsy.

Hydroxychloroquine is rarely associated with cardiomyopathy.

Congestive heart failure occurs in about 10% of patients with SLE and is usually secondary to hypertension, coronary artery disease, medication toxicity, or renal disease. Dilated cardiomyopathy or hypertensive heart disease typically develops. Both systolic and diastolic dysfunction may be seen in patients with SLE on echocardiography.
The second answer above is true. Many patients with SLE have heart valves with fibrinous lesions, a noninfectious condition known as atypical verrucous endocarditis or marantic endocarditis and initially described in 1924 by Libman and Sacks. Transthoracic echocardiography does not always show it. Estimates of the prevalence of Libman-Sacks endocarditis in SLE vary widely depending on how the condition is assessed. Valvular abnormalities are seen in 9% to 28% of patients with SLE by transthoracic echocardiography, in 53% to 73% by transesophageal echocardiography, and in 13% to 74% on autopsy.

Lesions are most common on left-sided valves, particularly the ventricular surface of the posterior mitral valve leaflet. The lesions are histologically similar to those seen with nonbacterial thrombotic endocarditis. Other valves may also be affected. Histologically, the lesions contain immunoglobulin deposits, indicating their autoimmune pathogenesis. On echocardiography, valvular masses and valve leaflet thickening are typical but are not pathognomonic in patients with long-standing SLE. Antiphospholipid antibodies may contribute to the pathogenesis of Libman-Sacks endocarditis. Many studies found an increased prevalence of valvular disease in patients with antiphospholipid antibody syndrome. Reisner et al found that about 32% of patients with primary antiphospholipid antibody syndrome had Libman-Sacks lesions as seen by echocardiography. Ziporen et al found antcardiolipin antibody by histology in the affected valves of patients with antiphospholipid antibody syndrome. However, Gleason et al found that Libman-Sacks endocarditis is often found in patients without antcardiolipin antibodies.

Chronic Libman-Sacks endocarditis can scar valves and lead to valvular dysfunction. Although valve disease in SLE is usually asymptomatic, valve replacement surgery may be necessary in patients with hemodynamically significant valvular dysfunction. Valvular lesions may embolize or become infected. Therefore, patients should receive antibiotic prophylaxis against infective endocarditis before undergoing invasive procedures associated with bacteremia, although no strong evidence supports this practice.

CORONARY ARTERY DISEASE IN SLE

Which of the following about coronary artery disease in SLE are true?

- It is uncommon
- It is not fully explained by traditional risk factors
- It is a leading cause of morbidity and mortality
- It is rarely seen in patients younger than 55 years

The second and third answers are correct. Common and serious. SLE causes accelerated atherosclerotic coronary disease and cerebrovascular disease, especially in younger age groups (35–49 years). Coronary artery disease is a leading cause of morbidity and death in this age group and accounts for up to 30% of all deaths in patients with SLE. The number of deaths due to atherosclerotic cardiovascular disease in patients with SLE is about equal to the number of deaths due to active SLE itself.

From 6% to 15% of patients with SLE have angina or a history of myocardial infarction. Subclinical atherosclerotic disease is more common: up to 40% have preclinical atherosclerosis that can be seen by carotid ultrasonography and 31% have coronary atherosclerosis that can be seen by electron beam computed tomography. Other noninvasive methods such as single-photon emission computed tomography perfusion imaging are commonly abnormal in patients with SLE who have no symptoms of cardiovascular disease, although coronary angiography is often normal in the same subset of patients.

Traditional risk factors do not fully account for the premature coronary artery disease in SLE patients. A suspected culprit is chronic glucocorticoid treatment, which can cause dyslipidemia, increased blood pressure, hyperglycemia, and increased homocysteine levels. Other factors, however, probably also play a role.

Congestive heart failure occurs in about 10% of patients with SLE.
Chronic inflammation contributes to artery disease
Autoimmunity and subsequent inflammation are also likely to be important in the pathogenesis of premature cardiovascular disease in SLE: immune complex deposition in the endothelium probably causes intimal injury and triggers accelerated atherosclerosis.32

Chronic inflammation is associated with the development and progression of atherosclerosis: patients with SLE who develop premature atherosclerosis have higher disease activity, longer duration of disease, an increased acute-phase reaction (measured by elevated levels of tumor necrosis factor, C-reactive protein, and fibrinogen), and less-aggressive immunosuppressive therapy.24,33 Activated complement products and autoantibodies to endothelium, high-density lipoprotein, and phospholipids have been suggested as SLE-related risk factors for atherosclerosis.34–37

On the other hand, young women with SLE have coronary artery narrowing secondary to atherosclerosis but without inflammatory changes or vasculitis visible on histologic study.38

Antiphospholipid antibodies also play a role in the pathogenesis of accelerated atherosclerotic disease in SLE.39 Part of an antibody may cross-react with oxidized low-density lipoprotein (LDL): autoantibodies to oxidized LDL independently predict progression of atherosclerosis in coronary and cerebral circulations.34–37,39

Mannose-binding lectins are liver-derived serum proteins involved in the innate immune response that may also contribute to SLE and atherosclerosis. Variants of mannose-binding lectin alleles are associated with an increased risk of arterial thrombosis in patients with SLE: patients with defects in mannose-binding lectins have earlier and more severe atherosclerotic disease than patients with normal mannose-binding lectins.40

Treat SLE patients as being at high cardiovascular risk
Because SLE is a significant coronary risk factor independent of other cardiovascular risk factors, prevention goals should be similar to those for patients with diabetes mellitus.41 Physicians should recognize the increased risk, minimize traditional risk factors, address disease-specific potential risk factors, and be willing to refer for a cardiac evaluation.9

Aspirin. Although no controlled trials have been done in SLE patients, daily low-dose aspirin is recommended.9,41

Try to limit glucocorticoids to the lowest possible maintenance dose.
Hydroxychloroquine. All patients should be considered for treatment with hydroxychloroquine, as it reduces SLE exacerbations and has modest antilipidemic, antithrombotic, and anti-inflammatory effects.9,24,42,43 However, the cardiovascular effects of hydroxychloroquine are only modest, and its direct effect on cardiovascular outcomes is unclear.

Statins. No specific studies have examined the use of statins for coronary artery disease in patients with SLE. However, the benefits of statins in the general population have been well established, and these drugs should be used as appropriate for patients with SLE.

Folic acid supplementation should be given for high homocysteine levels.29

CONDUCTION DISTURBANCES IN SLE

Many conduction abnormalities have been reported in SLE, including bundle branch block, atrial fibrillation, and first-degree, second-degree, and third-degree atrioventricular block. Some studies found evidence that arrhythmias are directly related to structural damage to the conduction system.44,45 Others found that autonomic dysfunction in SLE is related to heart rate variability.46–48 Arrhythmias are often secondary to underlying coronary artery disease or cardiomyopathy.

The neonatal lupus syndrome involves conduction abnormalities, usually in the form of congenital heart block, in children born to mothers with SLE.49

COMMENTS

• SLE can have serious cardiovascular complications.
• Internists and cardiologists should consider SLE in the differential diagnosis of a patient with the new onset of chest pain.
The diagnosis of SLE can be challenging, especially in young women of African descent.

- The diagnosis of SLE can be helpful to all physicians given the complexity of the disease; however, knowledge of the classification criteria of SLE can be helpful to all physicians.

# REFERENCES


ADDRESS: Emilio B. Gonzalez, MD, Division of Rheumatology, Department of Internal Medicine, The University of Texas Medical Branch, Galveston, TX 77555-1165; e-mail ebgonzal@utmb.edu.

Copyright Compliance and Bulk Reprints

Permission to reproduce articles from the Cleveland Clinic Journal of Medicine may be obtained from:
Copyright Clearance Center
1-800-982-3887, ext. 286
marketing@copyright.com
www.copyright.com

Bulk reprints of articles may be ordered directly from:
Cleveland Clinic Journal of Medicine
tel 216-444-2661
fax 216-444-9385
ccjm@ccf.org

We Welcome Your Letters

WE ENCOURAGE YOU TO WRITE, either to respond to an article published in the Journal or to address a clinical issue of importance to you. You may submit letters by mail, fax, or e-mail.

Please be sure to include your full address, phone number, fax number, and e-mail address. Please write concisely, as space is limited. Letters may be edited for style and length. We cannot return materials sent. Submission of a letter constitutes permission for the Cleveland Clinic Journal of Medicine to publish it in various editions and forms.

MAILING ADDRESS
Letters to the Editor
Cleveland Clinic Journal of Medicine
9500 Euclid Ave., NA32
Cleveland, OH 44195
FAX 216.444.9385
E-MAIL ccjm@ccf.org