Clinicopathological Conference

Sudden Death in a 55-Year-Old Woman With Systemic Lupus Erythematosus

Michael H. Kim, MD; Gerald D. Abrams, MD; Perry G. Pernicano, MD; Kim A. Eagle, MD

Case Presentation (Michael H. Kim, MD)

A 55-year-old woman with systemic lupus erythematosus (SLE) and hypertension was admitted for evaluation of a 1-week history of dyspnea and pleuritic chest pain. SLE was diagnosed 3 years ago and manifested as rash, recurrent angioedema, and arthritis. Maintenance therapy with continuous prednisone (10 to 50 mg/d) and briefly with methotrexate for 1 year controlled disease manifestations.

Two months before admission, she developed increasing fatigue and malaise. One week before admission, a mild, nonproductive cough and chills were noted. Over the next several days, she developed progressively increasing dyspnea on exertion and bilateral, sharp, anterior chest pain that worsened with inspiration, supine position, and movement.

The remainder of the past medical history was notable only for a miscarriage. Family history was unremarkable. The patient was a retired bookkeeper. She had smoked one-half pack of cigarettes per day for 20 years and had 1 alcoholic drink per day. There was no history of illicit drug abuse. Medications at the time of admission were prednisone 10 mg and sustained release nifedipine 60 mg daily. The patient was allergic to penicillin.

On physical examination, the patient was in moderate respiratory distress. Blood pressure was 160 to 180 over 90 to 105 mm Hg, heart rate was 120 bpm, respiratory rate was 30 to 40 breaths per minute, and temperature was 99.1°F. The neck veins were flat. Lung sounds were decreased halfway up on the left and one third of the way up on the right. No evidence of consolidation was noted. A loud, 3-component pericardial friction rub was heard. No murmur or gallop was appreciated. A pulsus paradoxus was not present. No active synovitis or joint findings were noted. Pertinent laboratory findings on admission are noted in the Table. The ECG on admission showed sinus tachycardia at 120 bpm.

Hospital Course

The patient was placed on oxygen with a 4-L nasal cannula with an oxygen saturation of 96%. A thoracentesis revealed bright-red blood. The rhythm was initially sinus, then junctional bradycardia.

Over the next several days, she developed progressively increasing dyspnea and pleuritic chest pain prompting transfer to the intensive care unit. Vital signs and physical examination were unchanged except for bradycardia at 58 bpm. An ECG showed deep T-wave inversions in leads V1 through V3. An aspirin and antibiotics (ofloxacin and erythromycin) were administered. A ventilation-perfusion scan was indeterminate. Two episodes of sinus bradycardia to 40 bpm prompted treatment with atropine. A pulmonary angiogram showed no evidence of pulmonary embolism. Repeat transthoracic echocardiogram and chest radiograph were unchanged. Serial cardiac enzymes were within normal limits. Low-dose morphine and Toradol were administered with resolution of chest pain.

On the fourth hospital day, the original pleural fluid cultures grew Streptococcus pneumoniae. The patient was noted to be comfortable and without complaints. Ten minutes later, she developed sinus bradycardia to 38 bpm and became unresponsive. Pulses were not palpable. Despite aggressive resuscitative measures for pulseless electrical activity, the patient died.

Kim A. Eagle, MD: “Was a pericardiocentesis performed at the resuscitation attempt, and what was the rhythm?”

Michael H. Kim, MD: “Yes, a pericardiocentesis was performed, revealing bright-red blood. The rhythm was initially sinus, then junctional bradycardia.”
Radiographic Findings
(Perry G. Pernicano, MD)

The chest radiograph (Figure 1) shows markedly increased opacity in the left hemithorax with silhouetting of the left heart border and left hemidiaphragm and obliteration of the left costophrenic angle. Mild blunting of the right costophrenic angle is also present. These findings are consistent with a small right pleural effusion and a large left pleural effusion obscuring visualization of the left lung. By default, there must be at least associated passive (compressive) atelectasis, but other underlying pathologies, such as a neoplasm or pneumonia, cannot be excluded. Bilateral decubitus views of the chest did not reveal a significant free-flowing component to the effusions, suggesting that they are loculated. An ultrasound of the thorax to help guide thoracentesis confirmed multiple septations and loculations within the pleural effusions.

Laboratory Values

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood gas (room air)</td>
<td>pH 7.50/pCO2 31/pO2 64</td>
</tr>
<tr>
<td>WBC</td>
<td>12 300</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>30.5</td>
</tr>
<tr>
<td>Platelets</td>
<td>398 000</td>
</tr>
<tr>
<td>Differential</td>
<td>84% polymorphonuclear cells/10% lymphocytes</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>138</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>3.2</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>22</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>22</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.3</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>90</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>262</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>2.6</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>1.9</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>103</td>
</tr>
</tbody>
</table>

WBC indicates white blood cell count; LDH, lactate dehydrogenase; and ESR, erythrocyte sedimentation rate.

Although the left heart border is obscured by the left pleural effusion, it is apparent from the multiple views that the cardiopericardial silhouette is enlarged. This could be due to true cardiac enlargement or a pericardial effusion. There is no evidence of pulmonary vascular congestion or edema.

In summary, given this patient’s clinical, laboratory, and radiographic findings, manifestations of SLE with a superimposed infection (pneumonia, empyema, and/or pericarditis) appear most likely.

Clinical Discussion (Kim A. Eagle, MD)

In general, we should consider broad categories in the differential diagnosis, including congenital disease, malignancy, immunologic disorders, collagen vascular disorders, infectious disorders, iatrogenic disorders, metabolic disorders, and so forth. Clearly, in this patient we seem to be wrestling with an immunologic process related to her lupus, a potential infection, and the relationship between them. The clinical presentation raises the specter of lupus-related conditions such as pleuritis, pericarditis, myocarditis, and associated coronary anomalies. In addition, the presence of a significant infectious process such as empyema or pneumonia must be entertained.

In patients with lupus, there is a pancarditis, which has been described.1 Myocarditis is usually subclinical and fairly infrequent in terms of its clinical manifestations. It is seen at autopsy, however, in as many as 40% of cases. Overt heart failure from lupus myocarditis is rather rare. Pericarditis is the most common cardiac manifestation. It is clinically present in 20% to 30% of cases. At autopsy, up to 75% of patients will show some signs of previously active pericardial inflammation. Interestingly, this inflammation may spread into the sinoatrial node or the AV node and cause arrhythmias. Large effusions and tamponade can occur.2 Purulent pericarditis may occur, particularly with encapsulated organisms, such as streptococcus.

The endocarditis of lupus is very interesting. Libman-Sacks endocarditis has been described,3 with verrucous, wartlike structures that are located particularly on the tricuspid, mitral, and aortic valves. These lesions rarely cause enough valvular dysfunction to be clinically manifest. They rarely embolize. Although Libman-Sacks endocarditis is an important finding in lupus, it is uncommon.

Other cardiovascular conditions should be mentioned. Lupus patients with active disease over time are more likely to develop premature coronary heart disease. This is due to a number of factors, most notably the coronary risk factors related to long-term steroid use. Thus, hypertension, obesity, and diabetes in combination with lipid abnormalities are common. Studies of large groups of lupus patients compared with age- and sex-matched control subjects have clearly shown much higher profiles for coronary risk in lupus patients on the basis of traditional risk factors.4 Hypertension is a very important and common manifestation in advanced lupus.

If one looks at causes of myocardial infarction in lupus, patients who have had infarction frequently have coronary thrombosis in the presence of antiphospholipid or anticardiolipin antibodies.4–6 Coronary thrombosis is an interesting entity in lupus. Some patients develop coronary thrombosis...
without apparent underlying coronary plaque lesions of any severity.\textsuperscript{4,7} The arteritis of lupus is rare, but coronary arteritis can be seen.\textsuperscript{8,9} The likelihood that a patient will develop coronary arteritis often reflects the duration and severity of their SLE. It is thought that small-vessel arteritis may be a cause of congestive heart failure, and there is a blending between small-vessel arteritis and myocarditis. Severe coronary heart disease and associated myocardial infarction, often at a young age, have been described.\textsuperscript{10–12}

Sudden death in lupus patients is uncommon in the literature. A few cases of sudden death not due to myocardial infarction have been reported.\textsuperscript{13,14} One of them was a patient with both myocarditis and thyroiditis who apparently had myocardial failure and arrhythmias leading to death.\textsuperscript{13} There was 1 patient who had fatal cardiac tamponade presumed to be secondary to anticoagulation and active inflammation in the pericardium.\textsuperscript{14}

One of the issues present in this case is that the patient had evidence of \textit{S} pneumoniae from a pleural specimen obtained on admission. In the antibiotic era, purulent pericarditis is very uncommon. The pathophysiology of purulent pericarditis is either the direct extension of an infection locally, such as pneumonia or empyema, into the pericardial space or, in some patients, extension from endocarditis. A perivalvular abscess may erode into the pericardial space, causing purulent pericarditis. Another mechanism is seeding from high-grade bacteremia, particularly in patients who have an effusion. Risk factors are continuous infection, burns, thoracic surgery, a preexisting effusion, uremia, and immune disorders including lupus.

SLE is clearly identified as a risk factor for purulent pericarditis, presumably because of the combination of pleural effusions, pericardial effusions, predisposition to infection, and diminished immune response. The treatment for purulent pericarditis must be aggressive. Obviously, effective intravenous antibiotics are essential. Pericardial drainage, which may require thoracotomy, is often essential for curing this infection. In a recent case series of purulent pericarditis, the organisms most commonly seen were streptococci, pneumococci, and \textit{Staphylococcus aureus}.\textsuperscript{15} Pneumonia was the most common cause locally. Complications of purulent pericarditis include tamponade, constriction, and death. In another case series of 12 patients, \textit{S aureus} was the most common organism, and in that series, staphylococcal pneumonia was frequently seen.\textsuperscript{16} One of those patients succumbed to the infection.

Recent case reports\textsuperscript{17–30} of purulent pericarditis that describe the types of patients and organisms are very interesting. Encapsulated organisms such as gonococcus, streptococcus, neisseria, meningococcus, candida, and \textit{Hemophilus influenzae} seem to be most commonly involved with purulent pericarditis. Lupus is represented several times as a predisposing medical condition. Burns, pulmonary tuberculosis, and renal transplants are other reported conditions. Most of these patients survived, although a number of them required emergency thoracotomy to drain the infected fluid surrounding the heart.

The period of fatigue and malaise, which lasted for 2 months in this patient, was probably a lupus flare. The development of a nonproductive cough and chills very likely represented a superimposed respiratory infection. The shortness of breath, pleurisy, and chest pain suggest that the patient had the pericarditis and pleuritis of lupus, but in addition, I believe there was secondary bacterial seeding with pneumococcus. The patient had a pleural tap on admission, which revealed fluid with white cells that were predominantly polymorphonuclear cells. It is said that the pleural fluid of lupus pleuritis more commonly will show monocytes and lymphocytes, and therefore the presence of white cells early in this patient’s course raised the suspicion of a superimposed infection. In a patient who was taking steroids and who had the possibility of an empyema, very aggressive treatment, including the possibility of open drainage of the pleural space, might have been considered, particularly because the pleural space was loculated. Her antibiotic choice initially was erythromycin only. She suddenly worsened ∼1 day after her antibiotic was discontinued. The worsened dyspnea and shortness of breath very likely represented an increased intensity in the infection. We cannot be sure that this patient did not also have some degree of myocardial ischemia, as noted by the T-wave inversions. This could be due to ischemia from thrombosis in the left anterior descending artery, underlying atherosclerosis that was then manifest in a very stressed patient, or possibly coronary arteritis.

The mechanism of sudden death potentially includes acute myocardial infarction, cardiac tamponade, and, less likely, pulmonary embolism or overwhelming sepsisemia. Given the findings obtained from pericardiocentesis, the patient appears to have died of cardiac tamponade, possibly related to the combination of lupus pericarditis and pneumococcal purulent pericarditis.

**Pathological Findings**

\textbf{(Gerald D. Abrams, MD)}

As predicted in the discussion, the patient’s underlying SLE was manifested mainly as an active pericarditis and pleuritis. Figure 2 shows the microscopic appearance of the pericardium. This pericarditis is characterized by a dense, chronic inflammatory infiltrate, mostly lymphocytes and plasma cells, underlying a layer of organizing exudate. The exudate in this instance is purely fibrinous (that is, nonpurulent). This rather bland chronic pericarditis is typical of lupus.

A similar chronic inflammatory process attributable to the patient’s SLE involved the pleura, but as predicted, we found a superimposed infectious process. A more-superficial exudate was found in the left pleural cavity. The leukocytes here were almost all neutrophils, in contrast to the lymphocytes and plasma cells associated with the more chronic lupus pleuritis; in fact, cocci were demonstrable in some parts of the exudate. Presumably this \textit{S pneumoniae} infection reached the pleural space via a pulmonary portal of entry.

The only other finding directly reflecting the patient’s SLE was a trivial one, the “onion skin” periarteriolar fibrosis seen in the spleen. At the time of the patient’s demise, the kidneys were not involved by lupus nephritis. They showed only the changes of nephrosclerosis correlating with the patient’s history of long-standing hypertension.

As expected, the immediate cause of death was found to be cardiac tamponade produced by hemopericardium. Figure 3 shows the surface appearance of the heart and aorta after draining the hemopericardium. Loculated, organizing hemorrhage is seen surrounding the base of the aorta and extending.
over the top of the heart. The wall of the heart was intact, and there was no gross or microscopic evidence of recent myocardial infarction. The coronary arteries were atherosclerotic, with ≈75% stenosis of the left main coronary artery and 50% stenosis of the left anterior descending artery. Microscopically, there was no evidence of arteritis or myocarditis.

The origin of the fatal hemopericardium could be traced, instead, to the proximal aorta. Figure 4 shows the opened aorta. Just above the aortic valve are 2 jagged intimal tears, which appeared to communicate with the localized periaortic hemorrhage. These were actually entry tears, leading to a dissection that extended the entire length of the aorta to the iliac arteries, and they involved the superior mesenteric and renal arteries as well. There was no evidence of preexisting aortitis, but a focal leukocytic reaction along the path of the dissection, as well as evidence of early organization of the periaortic hematoma, suggested that the patient sustained onset of the aortic dissection several days before her death, with the periadventitial hemorrhage being initially contained and then finally rupturing into the pericardial sac.

In summary, the patient had SLE manifested predominantly as lupus pericarditis and pleuritis, with secondary pneumococcal infection in the days before her death. Fatal cardiac tamponade was due to aortic dissection. This distinctly uncommon terminal event in SLE has been described previously.31–34 Interestingly, as with the patient we have discussed, these prior cases have also involved lupus patients who were hypertensive and who had been treated with regimens that included corticosteroids.

**Clinical Diagnosis**
Cardiac tamponade.
Lupus pericarditis and pleuritis in combination with pneumococcal purulent pericarditis.

**Final Diagnosis**
Cardiac tamponade.
Aortic dissection.
Lupus pericarditis and pleuritis.
Pneumococcal infection.

Figure 2. Photomicrograph of the pericardium. On the surface of the pericardium is a thick layer of organizing fibrin (top one third of the field). In the subjacent connective tissue is a chronic inflammatory infiltrate. This is nonpurulent pericarditis.

Figure 3. Anterior view of heart and aorta. The source of the hemopericardium around the base of the aorta is evident. This area of hemorrhage, which communicated with the aortic tears shown in Figure 4, had apparently been contained by periadventitial connective tissue, likely for several days before the final rupture.

Figure 4. Intimal surface of proximal aorta. Just above the aortic valve (bottom of field) are two jagged intimal tears (A and B). These tears were the entry sites of the dissection that ruptured into the pericardium.
Acknowledgment
The authors would like to acknowledge the assistance of Susan Duby in the preparation of this manuscript.

References
Sudden Death in a 55-Year-Old Woman With Systemic Lupus Erythematosus
Michael H. Kim, Gerald D. Abrams, Perry G. Pernicano and Kim A. Eagle

doi: 10.1161/01.CIR.98.3.271
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/98/3/271

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/