CLINICOPATHOLOGIC CONFERENCE

Sudden Death in a Young Woman With Sickle Cell Anemia

A 22-year-old woman with hemoglobin SS disease was admitted to Barnes Hospital on April 2, 1987. She died 3 days later.

Her history was remarkable for numerous painful crises characterized by back, leg, and shoulder pain. There was also a remote history of aplastic crises. Her complications of sickle disease included cholelithiasis, for which she underwent an uncomplicated cholecystectomy in 1982, and two episodes of pneumonia. In 1983, she had a therapeutic abortion, but in September 1985 she delivered a healthy infant. The pregnancy and delivery were complicated only by painful crises. She was treated with an oral contraceptive postpartum.

In January 1986, she complained of pain and swelling in the left thigh. Examination revealed tenderness and a possible cord. However, a venogram showed no evidence of deep venous thrombosis throughout the left calf or thigh, and the pelvic veins were patent.

After discharge she did well until April 1986, when she was readmitted in a painful crisis. The chest radiograph was normal. Arterial blood gas determinations with the patient breathing room air showed a pH of 7.38, a carbon dioxide tension (pCO_2) of 42 mm Hg, and an oxygen tension (pO_2) of 52 mm Hg; the pO_2 improved to 85 mm Hg on 2 liters of oxygen. Her hypoxemia was attributed to small-vessel ventilation-perfusion mismatch secondary to a vaso-occlusive crisis. She improved with fluids, analgesics, and oxygen and was discharged 6 days later.

The patient did well until April 2, 1987, when she was admitted with a several-day history of nonproductive cough and symptoms typical of one of her normal painful crises. She denied fever or chills. Her medications were folate and as needed meperidine hydrochloride and hydroxyzine pamoate. She was using a diaphragm for contraception; her last menstrual period had begun 4 days prior to admission. She admitted to occasional marijuana use.

Stenographic reports of weekly clinicopathologic conferences held in Barnes and Wohl Hospitals are published bimonthly in the *Journal*. Members of the Departments of Internal Medicine, Radiology, and Pathology of the Washington University School of Medicine participate jointly in these conferences. Kenneth M. Ludmerer, M.D., and John M. Kissane, M.D., Washington University School of Medicine, are the editors of this feature.

Physical examination revealed a well-developed, well-nourished woman in moderate distress secondary to pain. The blood pressure was 110/80 mm Hg, the pulse rate 108/minute, the respiratory rate 24/minute, and the temperature 38.4°C. Her sclerae were mildly icteric. Her neck was supple, and there was no jugular-venous distention, adenopathy, or thyromegaly. Auscultation of the chest revealed rales at the left base without egophony or dullness to percussion. The precordium was hyperdynamic, and a heave was noted along the left sternal border. The pulmonary artery was palpable. S_1 and S_2 were normal; a grade II/VI systolic murmur was heard at the left sternal border that radiated throughout the precordium. Results of abdominal and urogenital examinations were unremarkable. There was no clubbing, cyanosis, or edema.

Laboratory studies revealed a hemoglobin level of 9.3 g/dL, a hematocrit of 26.6%, and a white blood cell count of 16,400/mm^3 with a normal differential. The platelet count was 563,000/mm^3; the reticulocyte count was 17%. Howell-Jolly bodies and sickled red blood cells were present on the peripheral smear. Serum electrolytes and chemistries were normal except for a total bilirubin of 3.0 g/L and a lactic dehydrogenase of 491 IU/L. The result of a urinalysis was remarkable only for trace albumin. The prothrombin time was 17.0 seconds and the partial thromboplastin time 32.5 seconds. Arterial blood gas determinations on 2 liters of nasal prong oxygen revealed a pH of 7.39, a pCO_2 of 42 mm Hg, and a pO_2 of 97 mm Hg. The chest radiograph showed a left lower lobe infiltrate and a blunt costovertebral angle consistent with a small effusion; the heart size was considered mildly enlarged compared with that on previous examinations. An obstructive series revealed mildly dilated loops of large and small bowel with air fluid levels, suggestive of an ileus. The electrocardiogram showed sinus rhythm, poor R-wave progression, and nonspecific ST-T changes.

She was treated with intravenous fluids, narcotic analgesics, oxygen, and intravenous penicillin for presumed pneumococcal pneumonia. A chest radiograph on April 3 revealed that the left lower lobe infiltrate had not changed, but there was a new patchy infiltrate at the right base. Several blood cultures were negative except for one set, drawn in

the emergency room, which grew *Staphylococcus epidermidis*. On April 4, she developed a fever to 38.5°C. The white blood cell count was 23,000/mm^3 with 83% granulocytes and 17% lymphocytes. A chest radiograph showed bilateral lower lobe infiltrates (left greater than right), a left pleural effusion, and a questionable right pleural effusion; these findings were thought to be unchanged from the day before. Another obstructive series showed evidence of an adynamic ileus. Antibiotic coverage was switched from penicillin to intravenous erythromycin.

On April 5, 1987, she was found unresponsive, without respirations or pulse. Cardiopulmonary resuscitation was attempted but unsuccessful.

CLINICAL DISCUSSION

Dr. John Rogers: The outcome in this patient was very unfortunate, but I think it was predictable from what we know about her disease and its course up to this admission. This can be best understood by reviewing information regarding the natural history of sickle cell disease, information that has only become available by following large numbers of patients prospectively at certain sickle cell centers. First, however, I would like to make some points about the underlying pathophysiology of the disease.

The central problem in sickle cell anemia is that sickle hemoglobin polymerizes when it is deoxygenated; at oxygen tensions that are present in the venous capillaries, a substantial portion of sickle hemoglobin would be expected to be deoxygenated. Deoxyhemoglobin S polymers cause distortion of the erythrocyte (sickling); such a distorted cell is likely to occlude a capillary if it happens to be in one. With occlusion there is stasis, worsening local hypoxia, and more sickling. Fortunately, polymerization of deoxyhemoglobin S requires enough time that an erythrocyte can usually slip through the capillary before it sickles. It is reasonable to assume that any process that might slow the transit time of an erythrocyte through a capillary would adversely affect a patient with SS disease. Indeed, clinical data indicate that some patients have erythrocytes that are more likely to adhere to vascular endothelial cells, and that this adherence correlates with the severity of complications due to microvascular occlusions [1]. This phenomenon is *not* due to coagulation. Changes in the coagulation and fibrinolytic systems occur secondarily as a normal response to tissue injury; this is reflected by a number of reports in the literature documenting apparent increases in, for example, fibrinogen turnover during vaso-occlusive crises in sickle cell disease [2]. There is no credible evidence that blood coagulation is a major factor in the pathophysiology of sickle cell disease. Similarly, with the possible exception of a report from an uncontrolled study [3], there is no evidence that anticoagulants or antiplatelet agents have any role in the treatment or prophylaxis of complications of sickle cell disease.

This brings us to a point regarding our patient's course. She took oral contraceptives at one time following the birth of her child but then later changed to the use of a diaphragm for contraception. The change may have reflected an earlier view regarding oral contraceptives for women with SS disease. It has been asserted in the obstetrics literature that oral contraceptives are contraindicated for such women because "the risk of thrombosis may theoretically be enhanced" [4]. In fact, however, there is no scientific basis for this recommendation [5], and it deprives women who have a much higher risk of pregnancy-related complications of perhaps the most useful method of contraception. Any woman who takes oral contraceptives is at greater risk of thromboembolic disease, but there is no evidence that the presence of sickle cell disease has any effect on the incidence of those complications.

Internal medicine is a discipline founded upon the understanding of the natural history of disease; such an understanding was unfortunately lacking for sickle cell disease until relatively recently. Largely as the result of the establishment of comprehensive sickle cell centers, where patients were identified from community-wide screening and then followed prospectively, we now have fairly good data regarding the incidence of morbidity and mortality in sickle cell disease. My comments are taken largely from the studies of Powars and coworkers [6] in Los Angeles that have recently been summarized. These data involve 785 patients with SS disease who have been followed for 7,700 patient-years. Survival curves are provided for both SS disease and SC disease; the latter usually has a more benign course and provides a type of control for the effects of socioeconomic conditions on the lifespan of the population. These investigators found that about 20% of the patients with SS disease died in childhood (age less than 5), then there was a plateau with relatively few deaths until about age 20, when again an increased death rate was observed; the average lifespan for patients with SS disease was about 45 years [6]. When causes of death were considered, children usually died of complications of sickle cell disease, which included bacterial sepsis due to encapsulated organisms. In contrast, adults died from a broader spectrum of diseases. Some of these complications, such as chronic renal failure and cerebral vascular acci-

dents, could be related either to their sickle cell disease or to other medical problems, such as hypertension, that are common in persons from that racial and socioeconomic background. Other complications, such as chronic restrictive lung disease, acute chest syndrome (responsible for 30% of the deaths), and bone marrow infarction and embolism, were probably direct complications of sickle cell disease. It is interesting that patients from certain genetic backgrounds, as judged by restriction fragment length polymorphisms around the β-globin gene locus, are much more likely to have complications from vaso-occlusive disease [6].

The question of lung disease is most relevant to our patient's case. First, we can compare the relative frequency of occurrence of the "acute chest syndrome" (which I will argue our patient had) with that of painful crisis. About 70% of patients had one or more episodes of painful crisis during the survey period in Los Angeles, while 40% had the acute chest syndrome [6]; thus, this particular pulmonary complication is not unusual. (These figures also show that about 30% of patients with sickle cell disease have a relatively benign course.) A second statistic from that study addresses the question of whether pulmonary disease affects survival. About 5% of patients with sickle cell disease developed symptomatic chronic lung disease and cor pulmonale during the survey period [6].

Again, to concentrate on our patient's illness, we next should determine if the "acute chest syndrome" and chronic lung disease are part of the same process. We should begin with two reports that define the clinical entity of "acute chest syndrome" [7,8]; these are retrospective analyses, one from Johns Hopkins and one from England. This syndrome in a patient with sickle cell disease was defined clinically by the presence of chest pain or cough, fever, leukocytosis, and the appearance of an infiltrate on chest radiograph. Obviously, under these circumstances, the goal is to distinguish infection from pulmonary infarction secondary to vascular occlusion from sickled erythrocytes. Although one might think that the pulmonary circulation would not be a place to expect intravascular sickling, the pulmonary arterial system is very hypoxic and has relatively slow flow; this may explain why occlusion of pulmonary arterioles is not an uncommon problem. In children, this clinical presentation is usually associated with a positive culture for a bacterial pathogen, such as pneumococcus, and therefore is probably due to infection. In adults, the distinction is much more difficult; both series reported that most sputum cultures showed normal flora and blood cultures were negative. Angiography would be definitive in identifying vascular occlusion, but this was thought to be contraindicated because hypertonic contrast dye would predispose to more sickling [7]. All patients were hypoxic, but the degree of hypoxia was not helpful in distinguishing infection from infarction. Both series reported that antibiotic therapy did not shorten the duration of fever in their patients, a finding that is consistent with the inability to culture pathogens and that supports the concept that the syndrome in most adults is caused by vascular occlusion from sickling. Both series also reported that most patients were symptomatic, but about a quarter of them did not have infiltrates initially, probably because they were dehydrated. Almost all developed an infiltrate after hydration. The chest radiograph abnormalities were almost always basal, and, as one would expect, the duration of hospitalization correlated with the number of lobes involved.

In the acute chest syndrome, anticoagulation is not only of no therapeutic use but it might be harmful, since the vascular occlusion and ischemia would predispose to bleeding into the lung. The British report [8] advocates exchange transfusion for patients with the syndrome who are deteriorating clinically, since that approach would decrease the propensity for more vascular occlusion caused by sickling. At Barnes Hospital we use a slightly different approach for severely affected patients; we attempt to transfuse packed red blood cells to reach a normal or almost normal hematocrit.

There is good reason to believe that pulmonary vaso-occlusive events responsible for the acute chest syndrome in adults with sickle cell disease lead to chronic lung disease and pulmonary hypertension. Powars and colleagues [9] have attempted to define four stages of increasing severity in this syndrome of sickle cell chronic lung disease; their classification is somewhat helpful in evaluating our patient. Their earliest stage is defined by abnormal pulmonary function test results alone. At stage 3, hypoxia during stable periods is first observed; at this time, pulmonary fibrosis and right ventricular hypertrophy are to be expected. Recall that in 1986 our patient was observed to have had a pO_2 of 52 mm Hg while breathing room air, and at that time she was apparently not having pulmonary symptoms. Thus it is likely that she had some underlying lung disease of at least moderate severity.

What is most remarkable to me from the Los Angeles series is that 12 of the 28 patients followed prospectively had symptomatic myocardial infarction during an acute pulmonary event. All but one of these myocardial infarctions occurred in patients with stage 3 or 4 disease [9], but no coronary artery disease was found in any of these patients. Many of their patients died suddenly, either from a sudden

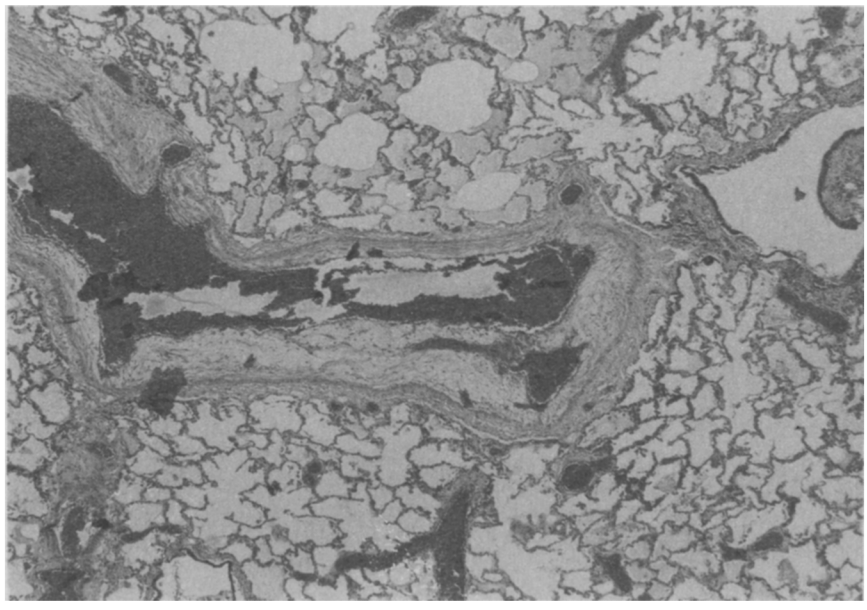

Figure 1. A large intrapulmonary artery shows partial occlusion by eccentric intimal hypertrophy consistent with old thrombosis; recent congestion is seen. The surrounding parenchyma is infarcted (hematoxylin and eosin stain; original magnification ×10, reduced by 30%).

episode of hypoxia or from a myocardial infarction [9].

I would summarize the information regarding sickle cell lung disease [9] as it pertains to our patient's case as follows. It is reasonable to conclude that chronic lung disease occurs as a direct result of multiple, probably often asymptomatic episodes of pulmonary arteriolar occlusion from sickling. Chest pain is episodic and often unreliable as a marker of pulmonary vaso-occlusion. Pathologic studies show that the vasculopathy is manifested by endothelial hyperplasia in small arterioles, accompanied by microinterstitial fibrotic lesions. Further, sickle cell lung disease with cor pulmonale, often associated with terminal adult respiratory distress syndrome, is the most frequent cause of sudden death in adults with sickle cell disease. Myocardial ischemia without coronary artery disease is a major contributor to the immediate death of the patients in this young adult population. The underlying lesion is pulmonary disease and pulmonary hypertension, but the persistent hypoxia somehow predisposes the patients to myocardial infarction and sudden death.

We have very little clinical data from our patient's previous admissions, but we know that she was hypoxic during a relatively asymptomatic time in 1986, and that she was again hypoxic when admitted this time with findings consistent with the acute chest syndrome: she had fever, cough, physical findings of pulmonary hypertension, and lower lobe infiltrates and cardiac enlargement on chest radiograph. She died suddenly. I think there is little question she had sickle cell lung disease; sudden death is part of that syndrome, and many patients with sudden death are found to have myocardial infarctions.

There are other, less likely, causes for her death. Cerebrovascular accidents are well described in adult patients with sickle cell disease [6], and we cannot exclude this possibility. I doubt that the cause for her ileus was likely to be a contributing factor; we have no reason to suspect a perforated viscus, pancreatitis, or gastrointestinal bleeding. We have no evidence for a source for sepsis. Sickle cell lung disease and its complications are the best explanation for her problems.

PATHOLOGIC DISCUSSION

Dr. Elizabeth N. Brunt: The primary pathologic findings at autopsy were in the lungs and consisted of numerous thrombi. The left lower lobe contained a large acute laminated thrombus; the surrounding parenchyma was infarcted (**Figure 1**). Throughout both lungs, several thrombosed arteries were seen. Some of the thrombi were organized and recanalized, others were more acute. The numerous thrombi were sufficient to account for respiratory failure and cor pulmonale. In addition, in the left upper lobe, pulmonary edema and marked congestion were observed.

On high-power examination, sickled cells were easily seen in capillaries. No evidence of interstitial fibrosis was seen. No evidence of bacterial or viral infection was noted, and results of Gram stains were negative.

Other significant findings at autopsy included the spleen; it was 23 g, 3.5 cm in length, and markedly fibrotic and atrophic. Histologic examination

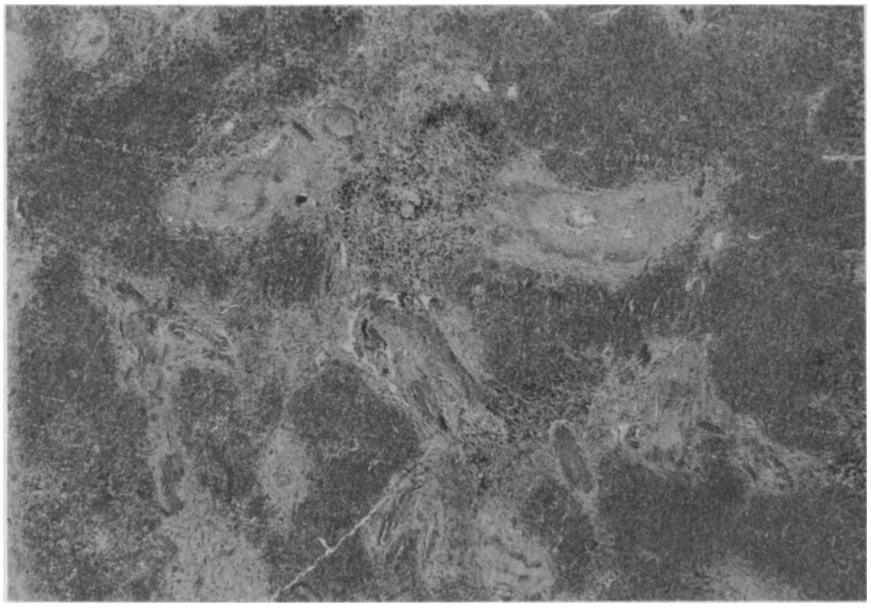

Figure 2. The spleen was atrophic and fibrotic. Numerous Gamna-Gandy bodies are present (hematoxylin and eosin stain; original magnification ×10, reduced by 30%).

revealed no remaining normal parenchyma; marked fibrosis and congestion were observed. Golden areas of hemosiderin consistent with Gamna-Gandy bodies were seen (**Figure 2**). These changes are consistent with the autosplenectomy known to occur in sickle cell disease.

The right colon was markedly dilated, but no evidence of perforation was seen. The kidneys showed a finding seen in patients with sickle cell disease: dilatation of the calyces. In addition, several glomeruli were congested. Sickling of red cells was apparent in these areas also. The liver was mottled and showed evidence of passive congestion histologically. There were dilated sinusoids; most likely these changes were secondary to heart failure from cor pulmonale. The heart was hypertrophic (270 g); there was no evidence of myocardial infarction. The bone marrow was markedly hyperplastic; 955 cells were erythroid. No evidence of cerebral vascular accident was seen in the central nervous system.

Final Pathologic Diagnosis: Sickle cell lung disease.

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