

Dyspnea with hemoglobin SC disease

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CASE PRESENTATION

LINDA S. BANG, MD: A 41-year-old African American woman with sickle cell disease presented to the Baylor University Medical Center emergency department with dyspnea and dry cough for 3 weeks and back, leg, and chest pain for 2 to 3 days. The hemoglobin SC disease had been first diagnosed during pregnancy. Pleural tuberculosis with a left-sided effusion had been diagnosed 2 years earlier, and she had been treated with 4 anti-tuberculosis medications. She also had had kidney stones and gallstones in the past. Her only operation was a hernia repair at age 38. Medications included rofecoxib, amitriptyline, and a recently completed 10-day course of trimethoprim and sulfamethoxazole for presumed tuberculous pleuritis. She worked for a laboratory, was separated, and had one daughter, who was well. She smoked about 10 cigarettes a day, drank alcohol occasionally, and denied intravenous drug use.

In the emergency department, her temperature was 97.4°F (36.4°C); heart rate, 121 beats per minute; respirations, 24 breaths per minute; and blood pressure, 110/80 mm Hg. Oxygen saturation was 87% on room air and 95% on oxygen via nasal canula. The pupils were equal and reactive to light. She had no precordial murmurs, rubs, or gallops. The lungs were clear to auscultation. No abdominal abnormalities were noted. The extremities showed no clubbing, cyanosis, or edema. The patient was alert and oriented with no focal deficits. Results of laboratory tests ordered in the emergency department are summarized in the *Table*.

After treatment with supplemental oxygen, intravenous fluids, and ketorolac tromethamine, the patient felt better and had decreased dyspnea and pain. When she walked, her oxygen saturation fell to 88%, and she became dyspneic, restless, and agitated and had a tonic-clonic seizure. She was given lorazepam and 100% oxygen via nonbreathing mask; she soon became bradycardic, diaphoretic, apneic, and pulseless. Cardiopulmonary resuscitation was initiated and she was intubated. Approximately 10 minutes later, heartbeats returned, and she was transferred to the coronary care unit. Her blood pressure was 127/77 mm Hg, her heart rate was 112 beats per minute, and she was unresponsive and intubated. The pupils were reactive, the neck was supple, and she had jugular venous distention to the angle of the jaw. She had a right parasternal lift and bilateral pulmonary wheezes. The abdomen was soft and slightly distended. The bowel sounds were normal. The extremities were cool but pedal pulses were satisfactory.

Table. Summary of laboratory values

Test	Emergency department		Coronary care unit	
	10:00 PM		7:00 AM	1:00 PM
pH	7.45		6.96	7.16
Pco ₂	28		30	26
PO ₂	65		266	95
O ₂ saturation (%)	94		98	95
Sodium (mEq/L)	136		143	141
Potassium (mEq/L)	5.1		7.2	3.9
Chloride (mEq/L)	106		110	109
Bicarbonate (mEq/L)	17		10	9
Blood urea nitrogen (mg/dL)	16		16	20
Creatinine (mg/dL)	1.0		1.0	1.7
Glucose (mg/dL)	121		280	383
Calcium (mg/dL)	9.0		8.5	9.4
White blood cells (×10 ³ /μL)	9.3		9.9	ND
Hematocrit (%)	28		20.7	29
Platelets (×10 ³ /μL)	116		68	ND
Reticulocyte count (%)	9.3		ND	ND
Total bilirubin (mg/dL)	1.6		0.9	ND
Alkaline phosphatase (U/L)	88		92	ND
Aspartate aminotransferase (U/L)	65		86	ND
Alanine aminotransferase (U/L)	31		48	ND
Troponin I (mg/mL)	<0.1		0.1	1.6
Creatine phosphokinase (U/L)	ND		53	706
Prothrombin time (sec)	ND		12.2	19.1
Partial thromboplastin time (sec)	ND		38.9	48.4

ND indicates not done.

An electrocardiogram showed sinus tachycardia with right bundle branch block, right atrial enlargement, and right ventricular hypertrophy with strain. A computed tomography (CT) scan of the head disclosed no abnormalities.

Additional laboratory tests were done after the patient arrived in the coronary care unit (*Table*). The peripheral smear

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showed rare hemoglobin C crystals, rare sickle cells, occasional schistocytes, and target cells. The sickle cell preparation yielded a positive result, and hemoglobin electrophoresis disclosed 51% hemoglobin S and 49% hemoglobin C. Tests for rheumatoid factor, HIV, and pregnancy were negative. The fibrinogen level was 75 mg/dL, thrombin time was >120 seconds, D-dimers were elevated at 3.2 to 6.4 µg/mL, and fibrin split products were >20 µg/mL. Urinalysis results included positive tests for protein, glucose, blood, and leukocyte esterase. Microscopic examination revealed 3 to 5 white blood cells and 30 to 50 red blood cells per high-power field. Urine cultures grew *Escherichia coli* and *Citrobacter freundii*; 1 of 2 blood culture bottles grew *Corynebacterium* sp. Sputum culture grew coagulase-positive staphylococcus.

The patient was given a dopamine infusion, a bicarbonate infusion, 4 units of packed red blood cells, 2 units of fresh frozen plasma, and cefepime and clindamycin intravenously. A few hours later, her systolic blood pressure fell to 60 mm Hg. Norepinephrine was given, another pulseless electrical activity arrest occurred, and she died.

IMAGING STUDIES

LINDA S. BANG, MD: The chest radiograph taken in the emergency department showed that the pulmonary trunk, both right and left main pulmonary arteries, and heart were dilated. The lung fields were clear. A spiral CT scan showed no emboli, but an infiltrate was present in the right upper lobe. An abdominal and lower extremity sonogram showed gallstones, a thickened gallbladder wall, and dilated hepatic veins and inferior vena cava. The fluid-filled bowel loops were mildly dilated. The spleen was not visualized. There were no deep venous thrombi.

SHELLEY A. HALL, MD: The patient's 2-dimensional echocardiogram showed normal left ventricular function, a very dilated right side of the heart, an enlarged pulmonary trunk, and tricuspid regurgitation. The maximum pulmonary artery systolic pressure was estimated to be 120 mm Hg. The valves were all structurally normal.

DIFFERENTIAL DIAGNOSIS

ROBERT D. BLACK, MD: This 41-year-old African American woman with hemoglobin SC disease had recurrent cough; dyspnea; and chest, back, and leg pain consistent with a vaso-occlusive crisis involving the lungs, vertebral bodies, and long bones of the legs. She was wheezing and developed progressive hypoxemia. She was anemic. The peripheral blood smear demonstrated sickle cells, and hemoglobin electrophoresis confirmed the diagnosis of hemoglobin SC disease. A CT scan showed a right upper lobe segmental infiltrate and interstitial infiltrates. She had markedly enlarged pulmonary arteries, consistent with pulmonary hypertension, but no evidence of pulmonary emboli. The electrocardiogram showed findings of right ventricular hypertrophy and strain, and the CT and echocardiogram indicated that she had chronic pulmonary hypertension. The pulmonary trunk was 40 mm in greatest diameter, an indication of significant pulmonary hypertension. She developed respiratory failure requiring mechanical ventilation, refractory metabolic acidosis, and refractory hypotension. She died within 24 hours of admission.

Possibly relevant findings in this case include a urinary tract infection, which could be a source of sepsis. Sputum culture was

positive for coagulase-positive staphylococcus, and the patient could have had staphylococcal pneumonia. She had a history of the tuberculous pleuritis, which should have been adequately treated. The positive blood culture probably represented a skin contaminant.

The most prominent feature of this case is that of severe pulmonary hypertension. The World Health Organization classification of pulmonary hypertension provides a framework for discussion of differential diagnoses. *Primary pulmonary hypertension* is an uncommon disease that occurs primarily in women in the third and fourth decades of life. Primary pulmonary hypertension, however, is a diagnosis of exclusion, and this patient had multiple potential secondary causes. Approximately 2% of cases of cirrhosis with portal hypertension are complicated by pulmonary hypertension. When the 2 coexist, the condition is known as *portopulmonary hypertension*. This patient had some mild elevation of liver function studies, but she had no evidence of cirrhosis.

The ingestion of any type of *anorexic agent* has been associated with a 6-fold increase in the risk of pulmonary hypertension. No information about this patient's body habitus or weight was given, but there was no history of ingestion of appetite suppressants. Pulmonary venous hypertension can be excluded since the echocardiogram showed no evidence of left ventricular dysfunction or left-sided valvular heart disease.

Pulmonary hypertension associated with *disorders of the respiratory system or hypoxemia* is a consideration, as the patient was a smoker and had evidence of interstitial lung disease. However, pulmonary pressures in the systemic range would be very uncommon, even in the most severe cases of obstructive lung disease and pulmonary fibrosis.

The most likely etiology of this patient's chronic pulmonary hypertension is *chronic thromboembolic disease*, related to either proximal pulmonary artery obstruction by recurrent pulmonary emboli or, more likely, obstruction of more distal vessels by in situ thrombosis and fat embolism associated with sickle cell disease.

An important question in this case is whether the CT scan was sufficient to exclude a clinically important pulmonary embolism. Until recently, there was some debate about the usefulness and accuracy of this technique. A review in the *Mayo Clinic Proceedings* reported that CT angiography using the pulmonary embolism protocol (also called helical or spiral CT) is an accurate, noninvasive method to diagnose pulmonary embolism at the main lobar and segmental pulmonary artery levels (1). The main criticism of this technique is that it may miss pulmonary emboli in more distal vessels at the subsegmental level. Standard pulmonary angiograms also will miss some of these smaller emboli. CT angiography has a reported sensitivity and specificity of 90% in the diagnosis of clinically significant pulmonary emboli. Although 5% to 10% of the studies are nondiagnostic, the same problem exists with standard pulmonary angiography.

Ryu et al reported that the interobserver agreement between readers of CT angiography was significantly better than the agreement between readers of ventilation/perfusion (V/Q) scans (1). A significant advantage of CT angiography is that it may provide an alternative diagnosis to pulmonary embolism, such as pneumonia, pleural effusion, adenopathy, or lung cancer.

Several outcome studies confirm the safety of withholding treatment in patients with negative CT scans (2–4). In a retrospective review of 143 patients, 113 patients had a negative CT scan (2). Of this group, 100 patients were followed up for 6 months, and investigators found no significant morbidity or mortality that could be attributed to pulmonary embolism.

A subsequent, somewhat larger retrospective review identified 126 patients who had a negative CT scan and compared their 6-month follow-up with that of >350 patients who had a V/Q scan (3). Only 1 of 78 patients who had a negative CT scan was found to have a microscopic pulmonary embolism at autopsy. It is unclear whether embolism contributed to the patient's death. A significant number of patients who had very low or low probability V/Q scans were subsequently found to have pulmonary embolism and deep vein thrombi. Garg et al concluded that helical CT was effective in excluding clinically significant pulmonary emboli.

The largest and most recent study was a prospective comparison of patients who had negative CT scans with those who had normal or low probability V/Q scans (4). Evidence for subsequent pulmonary emboli was found in only 1% of the patients who had a negative CT scan. This finding is comparable to that found in patients with a negative standard pulmonary angiogram. These studies show that helical CT is reliable for excluding clinically important pulmonary emboli.

This patient did not have CT scan evidence of acute or chronic pulmonary emboli. The etiology of her pulmonary hypertension relates primarily to her underlying disease process, sickle cell disease, which is caused by a group of hemoglobinopathies that are characterized by a single amino acid substitution in the beta globin chain. In hemoglobin S, the most common type of abnormality, valine is substituted for glutamic acid. In hemoglobin C, lysine is substituted at the same position. Patients who have hemoglobin S and hemoglobin A, typically in a 40%:60% ratio, have sickle cell trait. Although usually a benign condition, sickle cell trait has been associated with an increased risk of sudden death in military recruits undergoing vigorous training and in those who exercise vigorously at high altitudes. Patients with homozygous hemoglobin S disease, or sickle cell anemia, have the severest form of the disease. Compound heterozygosity for hemoglobin S and C is referred to as hemoglobin SC disease. The severity of hemoglobin SC disease is somewhere between the severity of sickle cell anemia and that of sickle cell trait.

The abnormal hemoglobin S tetramer is poorly soluble when it is deoxygenated. As a result, the deoxyhemoglobin S forms elongated, ropelike fibers that distort the red cell and cause sickling, which leads to decreased red cell deformability. While this polymerization is critical, an increased expression of adhesion molecules also contributes to the vaso-occlusive process. Several adhesion molecules have been identified; the most important one on the endothelium is named vascular cell adhesion molecule 1 (VCAM-1). The $\alpha_4\beta_1$ adhesion molecule is specific for the red cell membrane (5).

Although hemoglobin C does not undergo polymerization, the presence of hemoglobin C results in increased potassium and chloride transport out of the cell. The loss of potassium chloride causes dehydration of the red cell and a relative increase in the

concentration of hemoglobin S, which results in a greater propensity for polymerization and sickling (6). Hypoxemia and acidosis also increase polymerization, and these factors may have relevance in this case.

This patient suffered from *pulmonary complications of sickle cell disease*, which ultimately caused her demise. One of the more commonly reported pulmonary complications is pneumonia. Patients with sickle cell disease have an increased risk of infection because of their functional asplenia. Although pneumonia is very common in children with sickle cell disease, especially those <5 years of age, it is an uncommon complicating or precipitating factor for vaso-occlusive crisis in adults. Adult patients more often have pulmonary infarction due to in situ thrombosis, and they may suffer from embolic phenomena due to fat emboli and bone marrow infarction. These 2 processes result in what has been termed the acute chest syndrome.

The *acute chest syndrome in sickle cell disease* is defined by the National Acute Chest Syndrome Study Group as the onset of a new pulmonary infiltrate associated with chest pain, fever, tachypnea, and wheezing or cough (7). Among patients with sickle cell disease, acute chest syndrome is the most common form of acute pulmonary disease, occurring in 50% of all patients throughout their lifetime. It is the most common reported cause of death in patients hospitalized with vaso-occlusive crisis and is a significant risk factor for early mortality in these patients, accounting for 25% of premature deaths.

Microvascular infarction of the pulmonary parenchyma as a result of in situ sickling, occlusion, and thrombosis is the hallmark of the acute chest syndrome. The vaso-occlusive crisis begins with regional hypoxemia and the polymerization of hemoglobin S. Polymerization of hemoglobin S, red cell sickling, and increased expression of VCAM-1 lead to vaso-occlusive phenomena in various organs, particularly the bone marrow and lungs. Microvascular occlusion with bone marrow infarction can then lead to fat embolism. Concentrations of secretory phospholipase A₂ have been shown to be elevated in patients with vaso-occlusive crises, resulting in the liberation of free fatty acids from the bone marrow fat, which in turn leads to additional lung injury. Pulmonary infection can be a contributing factor. The pain associated with vertebral body infarction or rib infarction can lead to hypoventilation and atelectasis, which contribute to the increase in shunt and worsening regional hypoxemia (5, 8).

Studies supporting this model of the acute chest syndrome report increased plasma concentrations of VCAM-1 in patients during a crisis (5). Decreased concentrations of nitric oxide metabolites have been demonstrated as well, and nitric oxide has been shown in vitro to down-regulate the expression of VCAM-1. Patients with sickle cell disease who take hydroxyurea have a reduced expression of VCAM-1. Long-term hydroxyurea treatment has been shown to reduce the incidence of acute chest syndrome by 50%.

The National Acute Chest Syndrome Study Group analyzed 671 episodes of acute chest syndrome in 538 patients (7). A specific cause of acute chest syndrome was extensively investigated with blood cultures, bronchoscopy, and serology. The most common causes were fat and bone marrow embolism and infection, although infection was more common in the younger age group. When an infection was identified, the most common causative

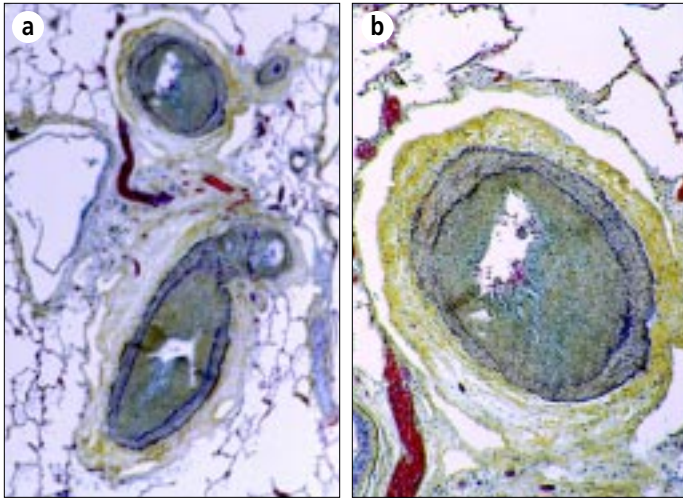


Figure 1. Photomicrographs of the lung in the patient described. (a) View of 2 muscular pulmonary arteries adjacent to a bronchus. The medial walls are thickened, and the intima contains fibrous tissue that has greatly narrowed the lumens. (b) A close-up view of one of the muscular pulmonary arteries shown in (a). Movat stains, $\times 40$ (a); $\times 100$ (b).

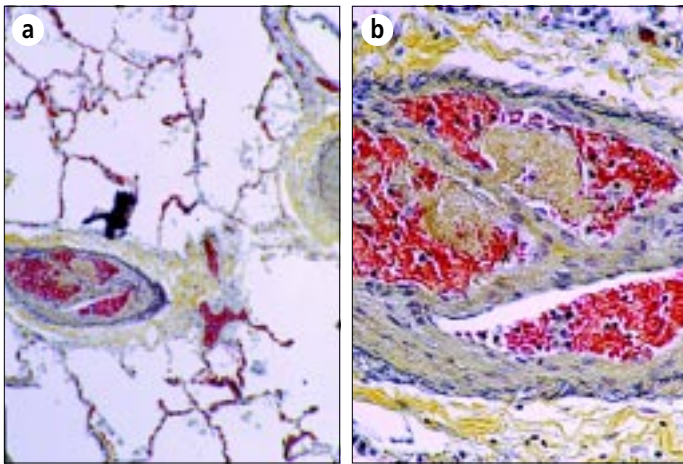


Figure 2. Photomicrograph of the lung showing a muscular pulmonary artery containing multiple luminal channels. (a) Low-power view. (b) Close-up view showing multiluminal channels containing red cells and a small fibrin clump in 2 of the channels. Movat stains, $\times 40$ (a); $\times 100$ (b).

organisms were *Chlamydia*, *Mycoplasma*, *Staphylococcus*, and *Streptococcus*. The study showed that 13% of patients required mechanical ventilation, and 22% of the adults had some type of neurological event, many of them being seizures. Among the adults in the study, there was a 9% mortality rate, which was attributed to fat embolism, cor pulmonale, or infection.

Repeated episodes of acute chest syndrome and repeated insults to the pulmonary circulation can lead to what has been termed *sickle cell chronic lung disease*, manifested by pulmonary hypertension and cor pulmonale in association with restrictive lung disease (9). Autopsy studies show obliteration of the pulmonary vascular bed, smooth muscle hypertrophy, and parenchymal fibrosis. The risk factors identified for the development of this syndrome over time are recurrent episodes of acute chest syndrome and vaso-occlusive crises. There is also a strong correlation with aseptic bone necrosis.

In a longitudinal study of 128 patients with the diagnosis of sickle cell chronic lung disease, patients were observed to progress

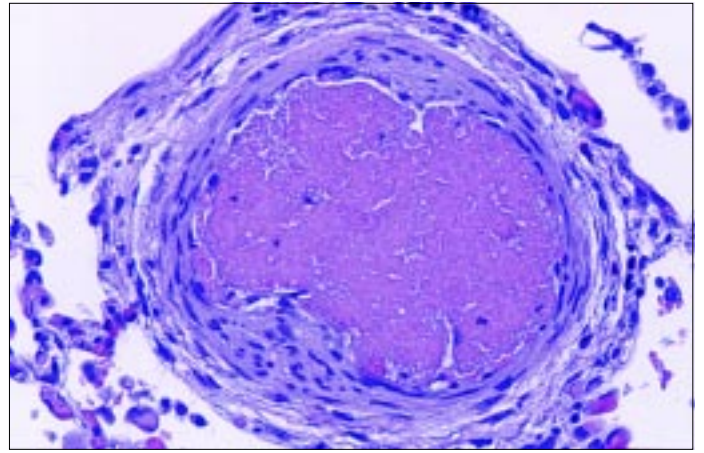


Figure 3. Photomicrograph of a small pulmonary arteriole containing a fibrin thrombus. Hematoxylin and eosin stain, $\times 400$.

through 4 stages of disease (9). These stages ranged from mild (mild chest pain and cough with mild pulmonary function study abnormalities but normal oxygenation and a mildly abnormal radiograph) to severe (prolonged, severe chest pain; dyspnea at rest; hypoxemia; severe pulmonary fibrosis; and severe pulmonary hypertension). In this study, the average survival after diagnosis was 5 years. Survival was reduced when compared with that of patients with hemoglobin SS disease who did not have the chronic lung disease. The investigators noted a high incidence of myocardial infarction without documented coronary artery disease; the etiology is unknown but may be related to right ventricular ischemia. The most significant risk factor for the development of sickle cell chronic lung disease was the total number of acute chest syndrome episodes that the patient had experienced.

To summarize, this patient had hemoglobin SC disease and evidence of recurrent chest syndrome. She probably had *sickle cell chronic lung disease*, as demonstrated by severe pulmonary hypertension and cor pulmonale and CT evidence of pulmonary fibrosis. Her acute illness was likely precipitated as an acute chest syndrome and vaso-occlusive crisis; she may have had staphylococcal pneumonia, although it is uncommon among adults. Urine culture results indicate possible urosepsis. The immediate cause of death was progressive right ventricular failure leading to refractory acidemia and pulseless electrical activity.

I predict that the autopsy findings will show chronic pulmonary hypertension with obliteration of the vascular bed, both the plexogenic and thrombotic pulmonary arteriopathy. Fat emboli may be present. I would expect evidence of pulmonary fibrosis, based on the CT findings. The right upper lobe infiltrate could represent pulmonary infarction or possibly staphylococcal pneumonia. Right ventricular hypertrophy and dilatation are likely, but I would not expect proximal thromboemboli. I will include the possibility of myocardial infarction simply because of the data from the previous study.

PATHOLOGY REPORT

WILLIAM C. ROBERTS, MD: The right pleural cavity contained 90 mL of straw-colored fluid, and the left had 20 mL of similar fluid. Numerous fibrous pleural adhesions were present bilaterally. No intrapulmonary masses, infarcts, or infiltrates were

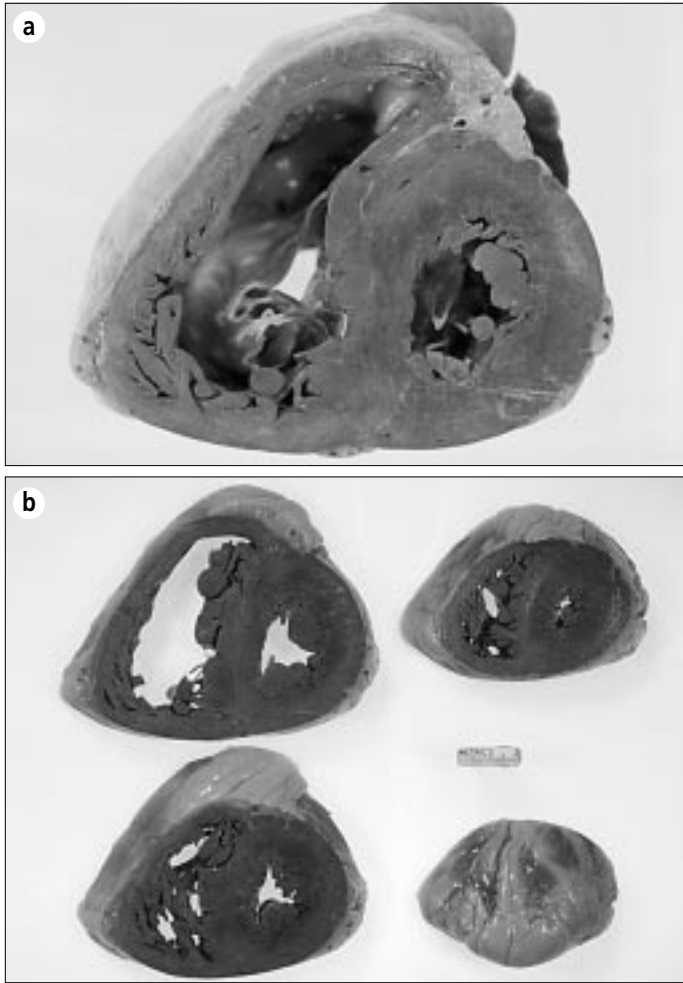


Figure 4. The heart in the patient described. (a) View of the base of the heart showing a very dilated right ventricular cavity and a thick right ventricular wall. The anterior portion of the ventricular septum is thicker than the left ventricular free wall, an occasional finding in cor pulmonale. (b) Cross-sectional views of the more apical portion of the heart, again showing a dilated right ventricular cavity with very prominent trabeculae in the right ventricular cavity.

present. The walls of the elastic and muscular pulmonary arteries were thickened, an indication of pulmonary hypertension (10). Many muscular pulmonary arteries also had thickened intima, which led to narrowing of many lumens (Figure 1). No plexiform lesions were present. A few muscular pulmonary arteries contained multiluminal channels, an indication of previous organization of thrombus or embolus (Figure 2). A rare muscular pulmonary artery contained a fibrin thrombus (Figure 3). Many alveolar capillaries were packed with erythrocytes, but

it was not possible to determine whether some were sickled. No bone marrow emboli were found.

The heart weighed 410 g. The right ventricular cavity was quite dilated (Figure 4) and its wall thick, typical findings of chronic cor pulmonale. The left ventricular wall and cavity were normal, as were the 4 cardiac valves and the epicardial coronary arteries. No myocardial lesions were present. No emboli were noted in the major pulmonary arteries, and no intracardiac thrombi were present.

In summary, the patient had morphologic evidence of chronic pulmonary hypertension that probably was reversible as evidenced by the absence of plexiform lesions. The presence of a rare thrombus (or embolus) in the small pulmonary arteries suggests that these thrombi were recurring and that many had organized into intimal fibrous lesions and some into multiluminal channels. No parenchymal lung disease was apparent. The heart was typical of chronic cor pulmonale.

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