Cryptococcal Pneumonia in a Patient with Sickle Cell Disease

Robert E. Hardy, M.D.,*1 Clinton Cummings, M.D.,†
Frank Thomas, M.D.,‡ and Duane Harrison, M.D.¶

We present the findings in a patient having sickle cell disease who developed multilobar pneumonia. Cultures of bronchial aspirates and histologic specimens grew Cryptococcus neoformans. There was neither spontaneous clearing of the infection nor a response to bactericidal antibiotics. The patient had no underlying malignant neoplasm or immunodeficiency as indicated by history, physical examination, and specialized tests of humoral and cell-mediated immunity.

Although the genus, Cryptococcus, is best known for its predilection to involve the central nervous system, primary pulmonary infection with this organism has been known since the report of Sheppe1 in 1924. A significant percentage of those who develop the infection have had underlying pulmonary disease, malignant neoplasms, or immunosuppression by drugs.2,3 Individuals with homozygous sickle cell disease are known to have an abnormal susceptibility to acute bacterial infections, particularly in childhood,4,5 however, impairment of cellular immunity in sickle cell disease has not been reported. To our knowledge, no previous cases of the association of primary cryptococcal pneumonia with sickle cell disease have been reported. The present report documents the first such case and discusses possible mechanisms leading to the infection.

CASE REPORT

A 33-year-old nonalcoholic black man who was not a drug abuser and who was known to be homozygous (98 percent of hemoglobin) for sickle cell anemia and to have cardiomyopathy was admitted to George W. Hubbard Hospital on Oct 23, 1984, complaining of increasing dyspnea, pleuritic chest pain, leg edema, a dry hacking cough, and fever for two weeks prior to admission.

One year prior to admission, the patient was documented to have marked cardiomegaly with a left ventricular ejection fraction of 30 percent. He had experienced two episodes of pneumococcal pneumonia in the past and recovered without sequelae. He smoked one pack of cigarettes per day and worked as a school bus driver. He had never been treated with glucocorticoid or other immunosuppressive agents and had no exposure to pigeons or other fowl.

Physical examination on admission revealed a temperature of 36.7°C (98°F), blood pressure of 120/90 mm Hg, and a respiratory rate of 22 breaths per minute. There were signs of congestive heart failure. The lungs revealed inspiratory and expiratory wheezing on the left. Both rhonchi and rales were heard on the right in the posterior basilar region. The chest roentgenogram obtained on admission is described in Figure 1. The liver was 18 cm in vertical span, and the abdomen was distended by the liver. The findings from the physical examination were otherwise unremarkable.

The initial culture of sputum grew +1 Staphylococcus hominis sensitive to multiple antibiotics. The white blood cell count (WBC) was 15,100/cu mm, with 79 percent segmented cells, 2 percent band

*From the Department of Medicine, Meharry Medical College, Nashville.
†Associate Professor, Division of Medical Oncology.
‡Assistant Professor, Division of Pulmonary Medicine.
§Assistant Professor, Division of Infectious Disease.
¶Medical Resident.

Reprint requests: Dr. Hardy, Meharry Medical College, 1005 D. B. Todd Blvd, Nashville 37205

FIGURE 1. Cardiomegaly, biventricular enlargement, and consolidation of right lung, especially lateral and superior segments.

FIGURE 2. Further consolidation and cavitation in right lung.
In addition to the problems of anemia and painful vaso-occlusion experienced in sickle cell disease, patients with this disorder are known to be highly susceptible to infection by encapsulated bacteria, but not to infections mediated by cellular immunity.\textsuperscript{4,5} Although the exact mechanism of immunodeficiency has not been elucidated, the process is primarily humoral.\textsuperscript{3,5} Investigators have found a deficiency in the ability of sickle cell plasma to opsonize bacteria such as pneumococci or Salmonella. Some have also found a decrease in C₃ and functional factor B and have correlated this with plasma-free hemoglobin levels.\textsuperscript{7} They have postulated the activation of complement by hemoglobin with the depletion of alternate-pathway proteins resulting in a deficiency of opsonization. The absence of a tetrapeptide, tuftsin, produced by the spleen has also been proposed as a mechanism of humoral immunodeficiency. The substance, which binds to heavy chains of immunoglobulin, has been found to be involved in phagocytosis by polymorphonuclear leukocytes and macrophages.\textsuperscript{8} Finally, abnormal immunoglobulin levels have been noted by some investigators.\textsuperscript{9} No decline in cellular immunity has been noted in sickle cell disease, and these individuals are not considered to be susceptible to fungal, protozoan, or mycobacterial infection.

Recently, Kerkering et al\textsuperscript{10} reviewed 43 cases of cryptococcal pneumonia. They observed the occurrence of the infection in the lungs of seven "normal" individuals without underlying malignant neoplasms or immunodeficiency. They concluded that the natural history of the disease in compromised hosts is extrapulmonary dissemination. Graybill et al\textsuperscript{11} have studied the course of pulmonary cryptococcal infection using the rat and nude mouse as models. Their results suggested the T cells as the main defect of immunity in susceptible hosts.\textsuperscript{12}

This patient showed no evidence of underlying T-cell deficiency, as demonstrated by normal T-cell levels, ratios, and total lymphocyte counts. Moreover, there was no history of prior opportunistic infections. Observed previous pneumococcal infections were in keeping with humoral (complementary) abnormalities reported to occur in patients with sickle cell disease. While possibilities of the subtle interaction of complement, cytotoxic antibodies, and T cells exist, there is little available evidence to substantiate such a mechanism in this case. It is possible that the occurrence of the infection was by chance, especially considering the presence of this infection in patients with no known underlying or predisposing disorders;\textsuperscript{13} however, the course of this patient's infection, unlike that of "normal hosts," did not spontaneously regress, and required antifungal treatment.\textsuperscript{14,15}

Thus, this case represents the first report of cryptococcal pneumonia in a patient with sickle cell disease. Although no overt deficiency in immunoglobulin, complement protein factors, or T-cell subpopulations were detected, alternate-pathway proteins may have been abnormal. The latter possibility, coupled with local factors, may have been significant as a cause of infection in this patient. This points up existing subtleties relative to components of the immune system. It should be recognized that such unusual infections

**Figure 3.** Significant clearing of infiltrate.

Five days following the initiation of therapy with amphotericin B, the patient's dyspnea and pleuritic chest pain decreased markedly. Eleven days later, the chest roentgenogram showed significant clearing of the infiltrate (Fig 3). By then the temperature had decreased to the range of 36.7°C to 37.2°C (98°F to 99°F). The WBC, which reached a zenith of 19,200/µm mm on Nov 1, decreased to 12,400/µm mm on Nov 12 and 8,400/µm mm by the time of discharge.

Other laboratory data and special tests such as pulmonary cytology, lung biopsy, special stains, and cultures were negative. Antibodies against Aspergillus were negative for \textit{A. fumigatus}, \textit{A. flavus}, and \textit{A. niger}; cryptococcal serology and spinal fluid for cryptococcal antigen were also negative; and the India ink preparation of cerebrospinal fluid revealed no cryptococcal organisms.

Immunologic parameters revealed an IgG level of 2,700 mg/dl (range, 639 to 1,349 mg/dl), normal globulin and complete and T-lymphocyte levels, an IgA level of 490 mg/dl (639 to 1,349 mg/dl), and an IgM level of 43 mg/dl (56 to 352 mg/dl). The total complement level, C₄₅, was 754 µg/ml (600 µg/ml to 1000 µg/ml); the level of C₅, was 1,410 µg/ml (1,200 µg/ml to 1,600 µg/ml); and the level of C₆, was 510 µg/ml (350 µg/ml to 600 µg/ml). The total lymphocyte count equaled 2,250/µm mm (normal, 1,000/µm mm to 4,500/µm mm); the total B-cell (B₁) percentage equaled 15.5 percent (5.6 to 16.0 percent); the total T-cell (T₁) percentage equaled 38.6 percent (36 to 50.5 percent); the T suppressor cell (T₅) percentage equaled 16.7 percent (16.8 to 28.6 percent); and the T/T₅ ratio was 2.31 (1.3 to 2.76). Skin tests to Candida and purified protein derivative of tuberculosis were negative.

Local infection of the catheter site required readmission to the hospital two weeks following the patient's discharge. After replacement, he returned to his home on antifungal therapy, which resulted in further improvement. On two follow-up visits the patient appeared to be asymptomatic with no complications. On the morning of Jan 30, 1985, the patient suffered sudden arrest at home. No autopsy was performed.

**Discussion**

\textit{Cryptococcus neoformans}, a potentially pathogenic fungus, can be isolated from a number of common environmental sources; however, few people develop systemic infections, and still a smaller number develop isolated pulmonary invasive cryptococcal infection. A significant proportion of these individuals appear to be so predisposed because of underlying pulmonary disease, the presence of reticuloendothelial neoplasia, or the use of immunosuppressive therapy.\textsuperscript{2,3,4,7}

**Chest / 89 / 6 / June, 1986 / 993**
may occur in patients with sickle cell disease. The course of this patient's illness may indicate that patients with sickle cell disease are another group requiring treatment with antifungal agents.

**References**


**Primary pulmonary hypertension is a severe disease with a generally fatal outcome. Although therapy with vasodilator drugs, such as hydralazine, can benefit some patients, deleterious effects have been reported.**

We report a case of severe pulmonary hypertension with secondary patency of the foramen ovale and atrial right-to-left shunt associated with systemic lupus erythematosus, in which hydralazine provoked a dramatic fall in systemic oxygen pressure. An irreversible cardiovascular collapse ensued. In this particular case, the decrease in oxygen pressure could have been due to an increase in the shunt through the patent foramen ovale.

**Case Report**

A 23-year-old woman was admitted to the hospital in March 1984 for dyspnea, chest pain, cough, and transient cardiovascular collapse. Systemic lupus erythematosus had been discovered at the age of 14 years (1975) when the patient presented with anorexia, weight loss, joint pain, myalgia, typical cutaneous signs, pericarditis, and Raynaud's phenomenon. Labial biopsy had confirmed an associated Sjögren's syndrome. The patient had received prednisolone since 1975. In November 1983, she began to experience progressively increasing exertional dyspnea; at this time the criteria of the American Rheumatism Association for the diagnosis of systemic lupus erythematosus, as well as native anti-DNA antibodies and low serum levels of complement, were found.

Studies of pulmonary function showed the following data: forced expiratory volume in one second, 2.45 L (predicted, 3.5 L); total lung capacity, 3.15 L (predicted, 4.3 L); and residual volume, 1.5 L (predicted, 1.37 L). The reduction in the ratio of the carbon monoxide diffusing capacity over the alveolar volume was 69 percent. A right cardiac catheterization showed a moderate increase in mean pulmonary pressure (37 mm Hg). Despite therapy with prednisolone (35 mg/day) and hydroxychloroquine (400 mg/day), dyspnea continued to increase and was present at rest on the day of admission.

Physical examination revealed a cyanotic, tachypneic young woman. Blood pressure was 130/100 mm Hg, heart rate was 115 beats per minute, and temperature was 37°C (98.6°F). Cardiac auscultation revealed a right ventricular gallop and an accentuated pulmonic closure sound. Jugular veins were distended; the liver was enlarged and painful. Crepitant rales were heard in both pulmonary bases. The spleen was palpable. No clinical sign of thrombophlebitis could be found.

Laboratory findings were as follows: hematocrit reading, 36 percent; red blood cell count, 4,290,000/cu mm; hemoglobin level, 12.4 g/dl; white blood cell count, 8,100/cu mm, with normal differential cell count; reticulocyte count, 260,000/cu mm; and platelet count, 11,000/cu mm. The haptoglobin level was normal, and antiplatelet antibodies were positive and of the IgG type. Prothrombin time was 13.8 seconds, with a control of 12.4 seconds. The fibrinogen level was 0.34 g/dl. The blood urea nitrogen level was 6 mmole/L (36 mg/dl); levels of serum electrolytes and creatinine were normal. The carbon dioxide level was 16 mEq/L. Plasma creatine kinase activity was normal, the lactate dehydrogenase level was 750 UI/L (normal, less than 240 UI/L), the aspartate aminotransferase level was 64 UI/L (normal, less than 20 UI/L), and the alanine aminotransferase level was 46 UI/L (normal, less than 20 UI/L). Urinalysis showed no proteinuria.

The electrocardiogram revealed sinus tachycardia and signs of right atrial and right ventricular hypertrophy, without right bundle-branch block. The heart was slightly enlarged on the chest roentgenogram, with prominent pulmonary arteries and basilar infiltrates. Arterial blood gas levels (on room air) as follows: arterial oxygen pressure were (PaO₂), 44 mm Hg; arterial carbon dioxide tension (PaCO₂), 17 mm Hg; and pH, 7.5. The PaO₂ rose to only 75

**Danger of Vasodilator Therapy for Pulmonary Hypertension in Patent Foramen Ovale**

J. F. Laine, M.D.; Michel Slama, M.D.; Patrick Petitpretz, M.D.; Philippe Girard, M.D.; and Gilbert Motel, M.D.

A 23-year-old woman with systemic lupus erythematosus was found to have severe pulmonary hypertension with secondary patency of the foramen ovale. Infusion of hydralazine increased the basal right-to-left shunt and resulted in a dramatic fall in arterial oxygen pressure, with subsequent irreversible cardiovascular collapse. Vasodilator therapy appears to be hazardous in patients with severe pulmonary hypertension and patent foramen ovale.

*From the Department of Cardiology, Hôpital Antoine Béclère, Clamart, France.*