ardous for the patient. A prominence of the alveolar lining cells was seen in our patient as was noted by Orwoll et al[9] with mitomycin, another alkylating agent. The histologic appearance is nonspecific. There were nuclear typia as can be seen in busulfan lung,[10] and this fact seems very important to note; is it the sign of drug toxicity?

There are very few bases for a pathogenic hypothesis; none has been proved. In any case, it seems obvious that the personal sensitivity of the patient is of prime importance. There is apparently no connection between the dosage of the medication received and the result, since Cole et al[11] report the case of a total dose of 4,130 mg at the time when the diagnosis was made.

The treatment also is worth study since corticotherapy is recommended. Littler and colleagues[12] think that steroids will be more successful at the beginning of the disease, before fibrosis appears.

Our patient came exactly within these limits; his condition improved considerably without treatment. We cannot prove that the result would have been even better with glucocorticoids.

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Aspergillus Vegetative Endocarditis and Complete Heart Block in a Patient with Acute Leukemia*

Stanislaw M. Mikulski, M.D.; Lillian J. Love, M.D.; Erick J. Bergquist, M.D.; Michael T. Hargadon, M.S.; Mark M. Applefeld, M.D.; and Wolfgang Mergner, M.D.

***Aspergillus flavus* vegetative endocarditis together with myocardial abscesses and pneumonitis developed in a patient with acute lymphocytic leukemia. The initial diagnosis was not suspected until ^{67}gallium imaging revealed a radiographically undetectable thoracic abnormality. Despite apparently "early" diagnosis, antifungal therapy was inadequate to prevent disruption of the bundle of His, complete heart block and death.**

Aspergillus flavus and *fumigatus* cause a significant number of infections in patients with acute leukemia, but endocarditis is a rarely reported manifestation of the infection in these patients. While leukemic patients with disseminated aspergillosis have developed myocardial abscesses caused by the fungus,[1-7] vegetative endocarditis has been reported previously in only four patients, and never in a patient with acute leukemia.[8-10]

Following is the report of a patient with pulmonary aspergillosis, vegetative *Aspergillus flavus* endocarditis and myocardial abscesses resulting in disruption of the bundle of His, complete heart block and death. The diagnosis of invasive pulmonary aspergillosis was unsuspected until a ^{67}gallium scan revealed abnormalities in the thorax not evident on chest radiographs. Bronchoscopic examination two weeks later established the diagnosis of *Aspergillus flavus* pulmonic invasion, but antifungal therapy then was inadequate to arrest the established cardiac infection.

Case Report

A 49-year-old previously healthy white man presented with the recent diagnosis of acute lymphocytic leukemia. The white blood cell count was 150,000 with 95 percent blasts, 1 percent granulocytes, hematocrit of 36 and a platelet count of 36,000. The patient was treated with methotrexate, vincristine, L-asparaginase and dexamethasone and by the fifth day had markedly hypocellular bone marrow with no circulating granulocytes. All antileukemic drugs except dexamethasone were discontinued. After initiation of treatment, the patient developed disseminated intravascular coagulation and mild glucose intolerance both of which resolved after three days of therapy with heparin and insulin. For the first eight hospital days, he received broad spectrum empiric antibacterial antibiotics for an unexplained fever which resolved by the fifth day. On the 14th day, the patient remained afebrile, but developed intractable hiccups

*From the Section of Infection Research, Baltimore Cancer Research Center, National Cancer Institute at the University of Maryland Hospital, and the Departments of Medicine and Pathology, University of Maryland School of Medicine, Baltimore.
Reprint requests: Dr. Mikulski, 27 Arverne Road, West Orange 07052

associated with left shoulder pain. A three hour ^{67}gallium scan demonstrated areas of increased uptake in the right hilum and lower left thoracic region while the routine chest x-ray film findings were normal. On the 18th day, tomograms showed a small retrocardiac density and, because the patient again became afebrile, antibiotics were reinstituted. On the 19th day, prior to scheduled bronchoscopy, the patient had an acute episode of chest pain and syncope associated with an incomplete right bundle branch block and ischemic changes in the inferior leads. He had no rise in serum cardiac enzymes, but later developed inferior Q waves. Because it was felt that the patient had sustained a myocardial infarction, but otherwise was clinically stable, bronchoscopy was postponed until the 34th day. At that time, a mucus plug was aspirated from the left lower lobe bronchus. Giemsa stains of the mucus plug and multiple mucosal biopsies revealed septated hyphae which were compatible with Aspergillus, so daily treatment with amphotericin B (0.6 mg/kg IV) plus rifampin (600 mg orally) were begun.[11] Fungal cultures of bronchoscopic material were negative but bacterial cultures grew *Serratia marcescens* for which the patient additionally received seven days of antibacterial antibiotics. On the 35th hospital day, a new murmur of aortic insufficiency was noted, but an echocardiogram and multiple blood cultures were negative. The possibility of endocarditis was considered, but multiple blood cultures had been negative for bacteria and an echocardiogram did not reveal vegetations. Aspergillus endocarditis was considered unlikely, but antifungal therapy was continued for the known pulmonary infection. On the 48th day, the patient appeared clinically well and was discharged to receive alternate day treatment with amphotericin (1.2 mg/kg) and daily rifampin. He was readmitted on the 53rd day after developing acute hypotension due to complete heart block. A temporary pacemaker was inserted and the following day a right upper lobe infiltrate developed. A transtracheal aspirate revealed *Serratia marcescens* for which he was again treated with antibacterial antibiotics. A repeat echocardiogram was negative for valvular vegetations. Five-fluorocytosine was added to the regimen of dexamethasone, ticarcillin, gentamicin, amphotericin B and rifampin, but the patient died from complete heart block and pacemaker failure the following day.

At autopsy, the patient's bone marrow was hypocellular with an increased percentage of lymphoblasts. There was an abscess cavity surrounded by bronchopneumonia in the right upper lobe and multiple abscesses in the left lower lobe. A large, friable vegetation was noted on the right aortic valve cusp with perforation of the right coronary cusp into the left ventricular cavity (Fig 1). An abscess cavity from the right sinus of Valsalva dissected through the most proximal portion of the interventricular septum, disrupted the bundle of His, and reached the septal leaflet of the tricuspid valve where a vegetation was seen (Fig 2). Vegetations were also noted on the anterior mitral leaflet. There were abscess cavities in the posterior left ventricular wall and interventricular septum. On histologic sections, hyphae were seen to disrupt the His bundle and to extend from the lumen of the right coronary artery into the left ventricular wall (Fig 3). Abscesses were also noted in the spleen and right kidney. *Aspergillus flavus* and *Serratia marcescens* were isolated from the vegetations, myocardial abscesses and areas of pneumonitis.

FIGURE 1. Aortic valve demonstrating eroded right coronary cusp with abscess cavity of sinus of Valsalva entering into the left ventricle and penetrating the interventricular septum.

FIGURE 2. Vegetative lesion on the septal leaflet of the tricuspid valve. This lesion was continuous with the abscess cavity extending from the right sinus of Valsalva. The opened right atrium is at the top of the photograph.

DISCUSSION

There is an increasing incidence of all fungal infections in patients with acute leukemia.[2-4,6] While most of these infections are caused by Candida, Aspergillus infections constitute a significant proportion of cases and there appears to be an increased relationship between Aspergillus infections and patients with acute leukemia relative to all cancer patients.[1-4,7]

It is unclear why patients with acute leukemia rarely develop infective endocarditis despite the high incidence of bacteremias and fungemias in that patient

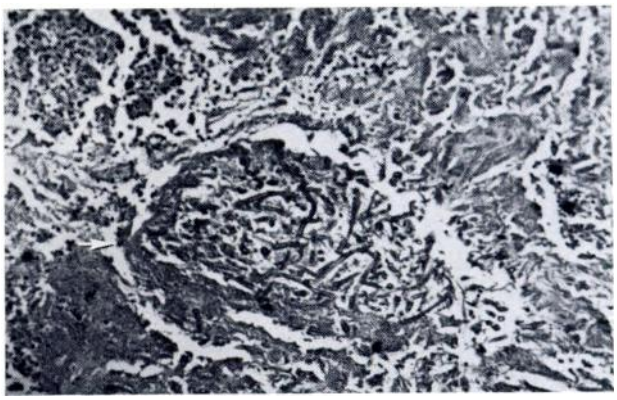

FIGURE 3. Photomicrograph of myocardial abscess caused by *A flavus* in the posterior left ventricular wall. Note the marked disruption of myocardial cells. Hyphae are seen in the lumen of the right coronary artery (*arrow*) and extend into the left ventricular wall.

population. In Bodey's[1] report of 38 cases of Aspergillus in 161 patients with acute leukemia, cardiac involvement was seen only as a manifestation of disseminated disease and consisted of myocardial abscesses. In an autopsy study of the hearts of 420 patients with acute leukemia, Roberts et al[5] did not describe a single instance of infective endocarditis. Only three patients in that series had endocardial vegetations and in none were organisms cultured or seen on microscopic examination. It is tempting to speculate that the explanation for the infrequent occurrence of infective endocarditis in patients with acute leukemia is that they are usually markedly thrombocytopenic during the times that most bacteremias and fungemias occur. Platelets are one of the major components of an infective vegetation—the others being fibrin and the pathogenic organism. In the presence of thrombocytopenia, it is conceivable that sterile vegetations do not form on cardiac valves. Without this nidus, infective endocarditis does not occur.[12] Additionally, platelets may play a permissive role in the aggregation of gram-positive organisms at the site of a sterile vegetation.[13] If these postulates are correct, then our patient had two unusual conditions which may have predisposed him to the development of infective endocarditis, *ie,* only moderate thrombocytopenia and disseminated intravascular coagulation. A recent report by Carrizosa et al[14] of an experimental model of Aspergillus endocarditis appears to support this hypothesis. These authors showed that Aspergillus endocarditis failed to develop in rabbits that had sterile thrombotic vegetations induced unless a source promoting continued platelet-fibrin deposition, *ie,* an intracardiac catheter, was present.

Since myocardial abscesses are the usual form of cardiac aspergillosis in patients with acute leukemia, it is surprising to find few reports of premortem cardiac signs and symptoms or electrocardiographic abnormalities. Meyer et al[3] and Young et al[7] have reported ST-T wave changes, atrial fibrillation, atrial fluttter and ECG changes compatible with myocardial ischemia or infarction in some patients with fungal cardiac involvement.

There is one reported case of complete heart block due to conducting system involvement by Candida in a patient with acute lymphocytic leukemia, but there are no previous reports of that phenomenon associated with Aspergillus infection in a patient with acute leukemia.[15]

Establishing the diagnosis of any Aspergillus infection in any patient is very difficult and rarely made premortem, in part because the majority of patients have sterile blood cultures[2-7] and proof of pulmonary involvement usually requires an invasive procedure. It is especially difficult when there are no clinical signs or symptoms except fever to indicate an infectious process. The diagnosis of Aspergillus pneumonia in this patient was established while evaluating intractable hiccups. A positive ^{67}gallium scan in the presence of a normal chest radiograph gave the first clue to an infectious intrapulmonary process. Forty-three percent of cancer patients reported by Bodey[1] to have proven pulmonic Aspergillus infections had no radiographic abnormalities. The positive ^{67}gallium scan in this patient prompted a more aggressive evaluation of this patient's pulmonary status than his clinical or radiographic condition would have indicated. Thus, the three-hour ^{67}gallium scan may be useful occasionally for evaluating other high risk patients with unexplained fevers.

Early diagnosis is essential for the successful treatment of all patients with a fungal infection and most important in the compromised patient. The subject of this case report had progressive disease while on adequate antifungal therapy and had received a total of 819 mg of amphotericin B by the time of death. He had *Aspergillus flavus* vegetative endocarditis, only rarely reported in the past and apparently never before recognized in a patient with acute leukemia.[8-10] Involvement of the cardiac conducting system by Aspergillus has not previously been reported as a clinical presentation of disease. The myocardial abscesses, not the vegetations, were the direct cause of death and illustrate the difficulty in treating abscesses successfully without surgical drainage. Thus, both early diagnosis and aggressive, adequate therapy are necessary for survival. This case shows the relative paucity of clinical manifestations and their late occurrence in the course of the disease. When they occur, it is usually too late for treatment to be effective.

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Pericardial Effusions in Sarcoidosis*

*Evlin Kinney, M.D.; Revathy Murthy, M.D.;***
*Gil Ascunce, M.D.;** Robert Donohoe, M.D., F.C.C.P.;***
and Robert Zelis, M.D., F.C.C.P.

A case of sarcoid pericarditis is presented. The associated pericardial effusion was a transudate with a low complement level. Investigating the prevalence of pericardial effusions in sarcoid by echocardiography, we found small effusions in 19 percent of 48 consecutive patients with sarcoid. Additionally, ten previously reported cases of symptomatic parietal pericardial sarcoid are reviewed.

Pericardial involvement by sarcoidosis has been reported infrequently and hence is an unfamiliar entity to most clinicians. The purpose of this article is to describe a case of pericarditis caused by parietal pericardial granuloma and to review the literature on this form of sarcoidosis.

Case Report

A 47-year-old black woman was admitted to the District of Columbia General Hospital on November 7, 1974 with dyspnea. She had been admitted elsewhere, 14 months previously, with fever, chest pain, palpitations, and dyspnea. She was found to have a pericardial friction rub and a large pericardial effusion by carbon dioxide angiography. She was treated with digoxin, diuretics, and bed rest, and was discharged four months later, asymptomatic. For the next 14 months she felt well. Then, two weeks prior to her current admission she again noted chills, fever and dyspnea.

Physical examination was remarkable for the following: her temperature was 101°F (38.3°C), she had labored respirations, and there was a 12 mm Hg pulsus paradoxicus, and an S_4 gallop. The arterial blood gas levels demonstrated Po_2 51 mm Hg and pH 7.49. Echocardiogram showed a large pericardial effusion.

Because the patient was extremely ill and the cause of her pulmonary and pericardial disease was unknown, it was decided to do a pericardial and pulmonary biopsy for diagnostic and therapeutic purposes.

At thoracotomy, 800 ml of straw-colored pericardial fluid was removed and a large pericardial window created. A biopsy of the lingula showed confluent, non-caseating granulomas. A biopsy of the parietal pericardium demonstrated numerous non-caseating granulomas.

The pericardial fluid was a transudate, with a total protein of 2.5 gm/dl, and a lactic dehydrogenase of 100 mg/L. There were 1,412 erythrocytes/ml and 36 leukocytes/ml, all of which were lymphocytes. The fluid was culture-negative for bacteria, fungi, tubercle bacilli, and viruses. The third component of complement (C3) was 12. Anti-heart antibodies were absent.

Postoperatively, the patient was given corticosteroids, but gradually worsening respiratory insufficiency developed and she expired five days later.

At autopsy, there was generalized fibrinous pericarditis, as well as fibrinous pleuritis. The right ventricular wall measured up to .4 cm in thickness. By microscopic examination, multiple non-caseating granulomas were found in the myocardium of the left ventricular free wall and in the parietal pericardium.

Discussion

The etiology of our patient's pericardial effusion has several potential explanations: left ventricular dysfunction, cor pulmonale, granuloma in the pericardium, or coincidental pericardial disease. In this patient, left ventricular dysfunction could not be discerned by physical examination, and at cardiac catheterization the mean pulmonary capillary wedge pressure was normal. Additionally, at autopsy there were very few left ventricular granulomas. Although cor pulmonale could have been present, in that the patient was severely hypoxemic at the time of right heart catheterization, there was only minimal pulmonary hypertension. Coincidental pericardial disease was effectively excluded in that the pericardial fluid was sterile for bacteria, fungi, and viruses. Additionally, she had no systemic disease with which pericardial involvement is associated. By microscopy, non-caseating granulomas were found in the visceral as well as the parietal pericardium. Thus, we conclude that this patient's pericardial effusion was due to the presence of pericardial granuloma *per se*.

The pericardial fluid was non-inflammatory: the fluid was a transudate, with small numbers of lymphocytes. Curiously, the third component of complement was 12 mg/dl, which is a low value for pericardial C3.[1] Of interest is that another sarcoid patient in our care in whom a thoracocentesis was performed had a pleural effusion which was a transudate with a low C3. Whether this combination of findings is characteristic of sarcoid effusions remains to be determined by further study.

Serosal involvement has been thought to be unusual in sarcoidosis.[2] This may not be entirely true. In a recent study, we found small pericardial effusions by echocardiogram in 19 percent of 48 consecutive patients with sarcoid, which could not be correlated with ECG, Holter, or thallium scan abnormalities, nor with the presence of left ventricular dysfunction by echocardiogram.[3] The apparent benignity of these effusions

*From the Department of Medicine (Cardiology)), the Milton S. Hershey Medical Center, the Pennsylvania State University, Hershey, and **The District of Columbia General Hospital, Georgetown Division, Washington, D.C.
Reprint requests: Dr. Kinney, Hershey Medical Center, Hershey, Pennsylvania 17023