Pneumocystis and Mucormycosis Pneumonitis*

Dennis L. Lombardi, M.D., James O. Mason, M.D.,
and Richard K. Hughes, M.D.

Two cases, one of Pneumocystis carinii pneumonia and the other of Absidia pneumonitis, are presented. Both are documented by appropriate laboratory studies. Both ended fatally in spite of seemingly appropriate current treatment. The Pneumocystis pneumonia was associated with prolonged corticosteroid therapy for progressive myositis and the Absidia infection was associated with uremia and corticosteroid administration. Infections from these opportunistic organisms may be seen with increasing frequency in patients on prolonged corticosteroids, immunosuppressive drugs, or chemotherapeutic agents.

We have recently cared for two patients, on corticosteroids, who had pulmonary infections from "nonpathogens" which were progressive and fatal in spite of seemingly appropriate current therapy. The organisms, Pneumocystis carinii and Absidia, are increasingly prevalent pathogens for which therapy in our hands seemed ineffective. The following two case reports are of concern in that they may represent a prelude to more frequent infections from these or other opportunistic organisms in association with drugs which decrease host resistance such as chemicals used in the therapy of malignancy, high dosage corticosteroids, and other immunosuppressive agents. The necessity for indefinite administration of corticosteroids and other immunosuppressive agents following organ transplantation may make the following two cases of particular concern to those active in organ transplantation.

CASE REPORT

CASE 1

A 51-year-old man was admitted to the University of Utah Medical Center in August of 1968, because of increasing muscle weakness for one year. A diagnosis of polymyositis was made by biopsy of skeletal muscle. Investigation for occult cancer was unrewarding. Methyprednisolone (84 mg per day) was started. He developed a Cushingoid appearance and his weakness continued. Three months later his pulse became irregular and an electrocardiogram showed changes consistent with myocarditis.

In January of 1969, he was admitted for the second time with profound muscle weakness. He had difficulty in holding his head up and was unable to walk up stairs. At the time of admission he was afebrile and his chest x-ray film was considered unremarkable. The following day his temperature rose to 103°F and a repeat chest x-ray picture showed an infiltrate in the right middle and lower lobes. His sputum contained gram-positive cocci. Penicillin was started; however his fever continued. Cephalothin and tetracycline were given. Dyspnea became increasingly prominent. After eight days, a chest x-ray film showed diffuse opacity in both lung fields (Fig 1). Steroids were continued and ten days after admission intramuscular pentamidine isothionate (280 mg per day) was started because of the possibility of a Pneumocystis pulmonary infection.

The patient continued to deteriorate, as manifested by stupor, tachypnea, dyspnea, and continued fever. A tracheostomy and open lung biopsy of the left upper lobe were performed. Microscopic examination of the lung showed diffuse interstitial edema, early fibrosis, local perivascular inflammation, intra-alveolar fibrin membranes, and Pneumocystis carinii (Fig 2). Following the lung biopsy, continuous ventilatory assistance was required with a volume respirator. He was continued on pentamidine isothionate in addition to cephalothin and tetracycline. The steroids were decreased. Pulmonary insufficiency continued in spite of improvement of the appearance of his chest x-ray picture. Resuscitation for a sudden cardiac standstill was unsuccessful. Pentamidine had been given for seven days.

At autopsy there was generalized skeletal muscle atrophy and histologic findings of polymyositis were seen. The heart was flabby and showed diffuse myocarditis. The lungs showed diffuse interstitial pneumonitis and Pneumocystis carinii were seen in alveoli. There was no malignancy.

DISCUSSION

There is lack of agreement on the taxonomic classification of Pneumocystis carinii. It cannot be cultured and has only been found in the lungs of man and experimental animals.1 Diagnosis is made by demonstrating the organism in lung tissue with Gomori's methenamine silver stain.2,3 Pneumocystis
PNEUMOCYSTIS AND MUCORMYCOSIS PNEUMONITIS

Clinical findings include severe dyspnea, nonproductive cough, fever, and decreased pulmonary compliance. The dyspnea is usually out of proportion to that expected from the appearance of the chest x-ray film. Diagnosis usually requires open lung biopsy; however, needle biopsy of the lung has been diagnostic.

Current preferred treatment is pentamidine isothionate (4 mg/kg/day). This agent has been used in the belief that Pneumocystis is a protozoan. Following administration of pentamidine reported mortality has dropped from 50 percent to 3 percent in infants. Pentamidine seems to be a folic acid antagonist and, therefore, serum folate decreases and megaloblastic anemia may develop. These side effects are usually reversible after administration of pentamidine is stopped. Concurrent administration of folic acid or folinic acid does not seem to decrease the effectiveness of pentamidine.

Intravenous administration of pentamidine may cause hypotension and, therefore, the intramuscular route of administration is preferred.

In the above patient, pentamidine seemed to effect partial resolution of the pulmonary infection as determined by serial chest x-ray pictures. However, marked myasthenia caused continued respiratory distress, the necessity for continuous ventilatory support, and finally death. Pulmonary sections at autopsy did appear to show decreased numbers of Pneumocystis when compared to the lung biopsy specimen. This may have been caused by the administration of pentamidine.

Case 2

This 23-year-old man was admitted to a local hospital in September of 1968 for evaluation of microscopic hematuria and pyuria which were first noted on a routine examination. His only symptom was mild fatigue. An open renal biopsy revealed foci of acute, subacute, and chronic glomerulonephritis. Uremia and anemia progressed rapidly and he was transferred to the University of Utah Medical Center one month later for evaluation, hemodialysis, and possible renal transplantation. He was started on prednisone (80 mg per day) with the hope of reversing his severe renal disease. After 43 days of prednisone he complained of cough, right-sided pleuritic chest pain and dyspnea. A chest x-ray film showed an infiltration at the base of the right lung and a right pleural effusion (Fig 3). Hemodialysis was administered. Fluid removed by thoracentesis was cultured and a Phycmycetes, Absidia, was identified. Closed thoracotomy was performed for empyema of the right hemithorax. In the middle of December, several intrapleural air fluid levels became apparent in spite of the large dependent tube in the right pleural space. Fever increased. A limited right thoracotomy was performed in order to lyse adhesions and improve pleural drainage. At operation a 3 x 4 cm piece of infarcted lung was found free in the pleural space. A defect in the lateral surface of the right lower lobe was apparent and an air leak was present. Histologic examination of the infarcted tissue again showed...
Absidia (Fig 4). The histologic diagnosis confirmed the cultures of the pleural fluid. The pulmonary specimen also grew out a coagulase positive, penicillin resistant Staphylococcus aureus.

Amphotericin B (60 mg per day after step-wise increases from 5 mg per day, increased at 5 mg per day) and nafcillin (Unipen) were given intravenously. Prednisone was discontinued. He became anuric and required two to three hemodialysis procedures each week. His fever decreased and he improved clinically; however, in January of 1969, he became febrile and stuporous.

Ability of the patient’s Absidia to grow in the presence of amphotericin B was tested. The organism was completely inhibited on a tryptose-case soy plate containing 100 μg/ml of amphotericin B while it grew on plates containing 50 μg/ml or less. Serum levels of amphotericin B were determined by a bioassay method. This demonstrated that following intravenous administration of 45 mg of the drug his serum level was .32 μg/ml 20 minutes after the infusion and .05 μg/ml after 24 hours. Amphotericin B serum levels were decreased to .04 μg/ml by hemodialysis. These studies demonstrated that amphotericin could not be delivered in adequate dosages to inhibit the Absidia. In spite of continued administration of amphotericin and pleural drainage a new air fluid level appeared in the apex of the right pleural space (Fig 5). A chest tube was inserted into this separate empyema cavity. The patient continued to deteriorate and died at the end of January, 1969. Permission for autopsy was refused.

**DISCUSSION**

Absidia appears to be a very destructive organism in the host with decreased resistance because of its tendency to vascular obstruction from invasion. Subsequent infarction may result. This occurred in case 2, as demonstrated in histologic studies.

Absidia is a genus of fungal organisms classified under the order of Mucorales and the class Phycomycetes. Other primary genera of this order are Rhizopus and Mucor. These organisms are lumped together under the disease called phycymycosis or mucormycosis. They are saprophytes which are ubiquitous in nature. The clinical picture of pulmonary mucormycosis consists of fever, leukocytosis, pleuritic chest pain, pleural friction rub and hemoptysis.11 Diagnosis can be established by culture of pleural fluid or necrotic pulmonary tissue on Sabouraud’s media.12 The fungus effects tissue in two ways:11,18 (1) by direct invasion of

**Figure 3** (Case 2). This chest x-ray film shows opacity at the base of the right lung where pleural fluid was recovered. The pulmonary parenchyma also appears opaque in this part of the lung. November 29, 1968.

**Figure 4** (Case 2). The elongated branching structures with dark margins in this piece of necrotic lung are Absidia (hematoxylin and eosin; × 375).

**Figure 5** (Case 2). Note free air in right costophrenic angle and air-fluid level at right apex. Lower half of right lung field is opaque. A tube is draining the right pleural space. Opacity at the left base was fluid. January 18, 1969.
tissues with subsequent inflammatory response, necrosis, and abscess formation, (2) by invasion of arterioles, which is followed by embolism, vascular obstruction, and infarction. The incidence of absidial infection is difficult to determine because few authors have differentiated the genera of the Mucor group. In one review there are 26 cases of pulmonary mucormycosis with only one classified as to genus (Rhizopus). Associated diseases in that review were leukemia and lymphoma, diabetes, multiple myeloma, burns, adrenal failure, renal failure, acidosis, and previous antibiotic therapy. Invasion by mucormycoses can be induced by experimental creation of diabetes with alloxan. In another review eight case of mucormycosis were found in 261 patients with leukemia. These cases were all subsequent to 1953 and perhaps reflect the increasing use of steroids and chemical agents since that time.

The relationship of steroids to the fungal infections has been studied by both experimental and case series studies. Corticosteroids decrease the inflammatory response of the host. Corticosteroid enriched media, however, have not enhanced fungal growth. In review of several series of patients with fatal mycoses, of 44 deaths, 31 of the patients were on steroids, and 37 were on antibiotics. One author feels that antibiotics alone enhance surface mycoses while antibiotics in conjunction with steroids favor deep mycoses. The former represents altered flora, while the latter reflects altered flora in a compromised host.

There is no current specific treatment for the mucor genera. Potassium iodide, nystatin and amphotericin B have been tried. Data from case 2 appears to demonstrate that amphotericin B could not have been effective in the dosages used against this Absidia. Toxicity limits the amount of amphotericin B which can be safely administered. Correction of diabetic acidosis may effect resolution of associated pulmonary mucormycosis.

References

Reprint requests: Lt. Lombardi, U. S. Naval Hospital, Box 263, Portsmouth, Virginia 23708