10 Wilson FN, Johnson FD, Barker PS: Electrocardiograms of an unusual type in right bundle branch block. Amer Heart J 9:472, 1934
11 Lasser RP, Haft JI, Friedberg CK: Relationship of right bundle branch block and marked left axis deviation (with left parietal or peri-infarction block) to complete heart block and syncope. Circulation 37:429, 1968
12 Watt TB, Freud GE, Durrer D, et al: Left anterior arborization block combined with right bundle branch block in canine and primate's hearts. An electrocardiographic study. Circ Res 22:57, 1968
13 Lopez JF: Electrocardiographic findings in patients with complete heart block. Brit Heart J 30:20, 1968
14 Watt TB, Pruitt RD: Character, cause and consequence of combined left axis deviation and right bundle branch block in human electrocardiograms. Amer Heart J 77:460, 1969
15 Rothfeld EL, Zucker R, Tiu R, et al: The electrocardiographic syndrome of superior axis and right bundle branch block. Chest 55:306, 1969
16 Lewis T: An address on certain physical signs of myocardial involvement. Brit Med J 1:484, 1913
17 Dressler W: Delayed conduction in the bundle branches: A report of two cases in which the P-R interval increased with changes from left to right bundle branch block. Amer Heart J 29:728, 1945
18 Rosenbaum MG, Lepeschkin E: Bilateral bundle branch block. Amer Heart J 50:38, 1955
19 Schloff LD, Adler L, Donoso E, et al: Bilateral bundle branch block: Clinical and electrocardiographic aspects. Circulation 35:790, 1967
20 Rosenbaum MB, Nau GJ, Levi RJ, et al: Wenckebach periods in the bundle branches. Circulation 40:79, 1969
21 Rosenbaum MB, Elizari MV, Nau GJ: Five cases of intermittent left anterior hemiblock. Amer J Cardiol 24:1, 1969

Deep Entomophthora Phycomycotic Infection Reported for the First Time in the United States*

*Herbert L. Eckert, M.D.,** George H. Khoury, M.D.,† R. Scott Pore, Ph.D.,‡ Enid F. Gilbert, M.D.,§ and James R. Gaskell, M.D.†*

A mediastinal phycomycotic infection in a Caucasian infant caused by Entomophthora was confirmed by culture and histologic examination of biopsy material. The patient had heart failure resulting from the invasive mediastinal mass, eosinophilia, and hyperglobulinemia. Unlike other cases of Entomophthora disease, usually confined to subcutaneous areas and limited to the tropics, this present case involved a deep infection in a patient who lived in a temperate zone. The disease was amenable to amphotericin B therapy.

Since 1956, reports on the occurrence of human infections caused by phycomycetes fungi, family Entomophthoraceae, have involved only residents of the tropics.[1-4] These infections were subcutaneous mycoses and, with the exception of a possible case reported by Ridley and Wise,[5] the involvement of deeper structures by Entomophthoraceae have not been reported. This case report represents an exception to the usual clinical and epidemiologic aspects of disease caused by an Entomophthora species, and describes a deep phycomycotic infection occurring in a Caucasian resident of the temperate zone.

Case Report

A previously well 15-month-old Caucasian boy was admitted to the hospital with a six-week history of croupy cough, weight loss, and irritability which had become progressively more severe. There was no history of contact with infectious disease or of any travel which might have contributed to the initial infection.

On admission, the patient appeared pale, listless, and extremely irritable. The respiratory rate was 35 per minute. The temperature was 38.2° C, pulse regular at 140 per minute and blood pressure 138/88 mm Hg. Expiratory wheezes were heard throughout both lung fields. The abdomen was distended, and a tender liver edge was felt 4 cm below the right costal margin. Hemoglobin and microhematocrit were 9.3 gm percent and 33 percent, respectively. The anemia was hypochromic and microcytic. The erythrocyte sedimentation rate was 63 mm per hour. The peripheral leukocyte count of 19,250 per mm^3 consisted of 49 percent neutrophils, 26 percent lymphocytes, 16 percent eosinophils, and 9 percent monocytes. The bone marrow demonstrated myeloid hyperplasia with an increased proportion of the eosinophil series and megakaryocytes. Humoral globulins were elevated as follows: IgG-2400 mg percent, IgA-96 mg percent, IgM-280 mg percent, $Beta_{1c}$-175 mg percent. The patient's phagocytes were able to reduce nitroblue tetrazolium. The patient exhibited a positive skin reaction to Candida antigen at a dilution of 1:10. After a sensitizing dose of 10 percent 2-4 dinitrofluorobenzene was applied, the patient demonstrated a positive reaction to the challenge dose of 0.02 percent. Cardiac radiography revealed generalized cardiac enlargement, bilateral pneumonic infiltrates obliterating the cardiac margins, a small amount of fluid in the left costophrenic angle, and marked pulmonary venous congestion in the left lung. There was evidence of left atrial enlargement. The ECG showed nonspecific T wave changes with diphasic P waves in the right precordial leads. Cardiac catheterization and pulmonary angiography suggested a posterior mediastinal mass displacing the left atrium and ventricle downward and anteriorly.

After his cardiac failure had been controlled, the patient underwent an exploratory thoracotomy which revealed a hard, posterior mediastinal mass invading the left main stem bronchus and pericardium. A biopsy specimen of the mass,

*From the Department of HEW, US Public Health Service, National Institute for Occupational Safety and Health, Appalachian Laboratory for Occupational Respiratory Diseases, and West Virginia University School of Medicine, Morgantown, West Virginia.
**Department of Medicine (Division of Preventive Medicine, West Virginia University School of Medicine, Morgantown.
†Department of Pediatrics, West Virginia University School of Medicine.
‡Department of Microbiology, West Virginia University School of Medicine.
§Department of Pathology, West Virginia University School of Medicine.
Reprint requests: Dr. Eckert, West Virginia University Medical Center, Morgantown 26505

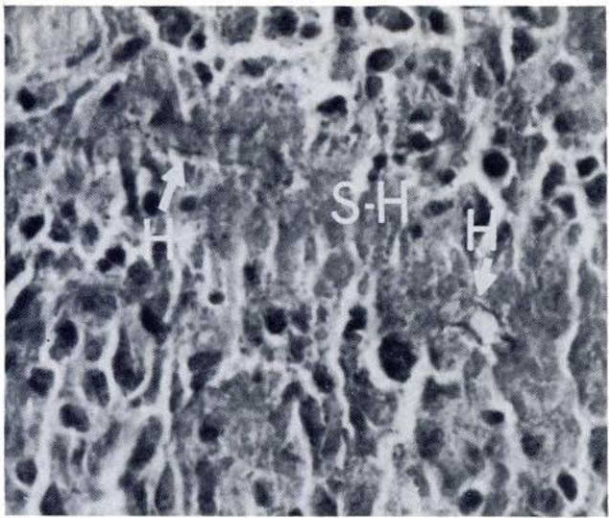

FIGURE 1. Mediastinal granuloma with Entomophthora hyphae fragments (H) and Splendore-Hoeppli phenomenon (S-H), PAS stain; (× 500).

suspended in sterile saline was inoculated onto Sabouraud-dextrose agar (Difco). From the morphology and projectile behavior of the conidiospores which lodged on the Petri dish lid, the agent was identified as the genus, Entomophthora. Species determination studies, still incomplete, eliminated the most familiar *E coronata* on the basis of absent fillous appendages surrounding the resting spore. Sputum, tracheal aspirate, and pleural fluid did not contain the microorganism.

The microscopic appearance of the mediastinal mass was that of a granulomatous reaction in which a dense fibrocytic and fibroblastic stroma was studded with numerous, small, round, and stellate foci. Central portions of the foci were filled with brightly eosinophilic material. Hyphae were enmeshed within the central granular eosinophilic material (Fig 1), a manifestation known as the Splendore-Hoeppli phenomenon.[6] The hyphae were thin-walled, 4 to 8 microns thick, and were most clearly defined in periodic acid-Schiff preparations (Fig. 2). In proximity to the granulomatous cores were giant cells which contained up to 40 nuclei and assumed a size as large as 50 microns.

The patient was given intravenous amphotericin B which was gradually increased to a daily dose of 1 mg per kg body weight until a total dose of 315 mg was administered over a 2½ month period. No protein was found in serial urinalyses; the BUN remained normal. Fever subsided within one week after the start of amphotericin B. At the termination of therapy, hemoglobin and microhematocrit values had increased to 12.0 gm percent and 38 percent, respectively. The erythrocyte sedimentation rate diminished to 12 mm (Westergren). The peripheral leukocyte count was 7,700 per mm^3 of which 36 percent were neutrophils, 52 percent lymphocytes, 1 percent eosinophils, and 11 percent monocytes. The state of hyperglobulinemia improved as follows: IgG-1300 mg percent, IgA-27 mg percent, IgM-300 mg percent, and $Beta_{1c}$-155 mg percent. The heart size became normal and the patient quickly regained his lost weight, his appetite, and usual activity. Fifteen months after termination of medication, there have been no signs of relapse.

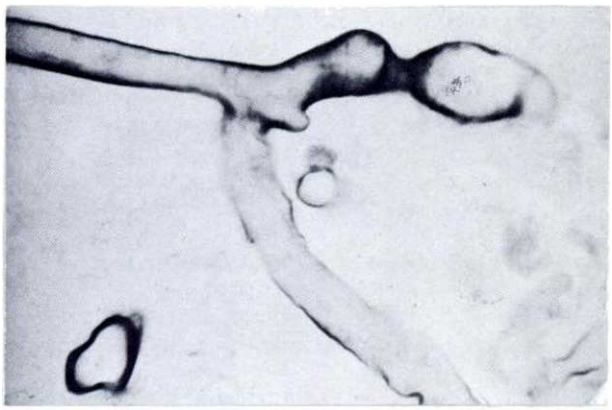

FIGURE 2. Smear from mediastinal granuloma showing Entomophthora hyphae, PAS stain; (× 2,000).

DISCUSSION

The unusual occurrence of a deep phycomycotic infection in a Caucasian infant from a temperate zone caused by Entomophthora was confirmed by culture and histologic examination of biopsy material from a mediastinal mass. Neither the circumstances relating to the initial infection nor the factors contributing to the marked severity of the disease could be ascertained. In contrast to infections by "opportunistic" fungi *ie*, mucormycosis, often a fatal disease of patients with severe underlying defects, the severe Entomophthora phycomycosis described in this case report involved an apparently previous healthy patient. Although it cannot be said with certainty that our patient may not have had an underlying defect, latent infection, or altered host defenses, he did however have the ability to produce functional IgG and IgM, and peroxidase activity was demonstrated in segmented neutrophils. Evidence of cellular immunity was also present. Nevertheless, an undetected defect may have provided the Entomophthora microorganisms on their initial introduction to assume the role of an "opportunistic" agent and induce the severe disease that was manifested. Regardless of the pathogenic or opportunistic status of the Entomophthora microorganism, there is no question that it was responsible for the serious disease desoribed in this patient.

It may be appropriate to note that Entomophthora species have been considered for use as biological agents for insect control.[7] As important as the technique of biological control of insects may become, the danger to the human host, exemplified by this present case, warrants more intensive investigation on the pathogenic potential of fungal insecticides before they are released for widespread use.

ACKNOWLEDGMENTS: We gratefully acknowledge Dr. Carl E. Johnson for referring his patient, Mr. Nicholas Hahon and Dr. Anthony Seaton for their critical review of the paper, the technical assistance from the staffs of the WVU Hospital Microbiology Laboratory and the Department of Pathology, and Miss Martha Saab for her typing skills.

REFERENCES

1 Joe LK, Eng, N-IT, Phoan A, et al: Basidiobolus rararum as a cause of subcutaneous mycosis in Indonesia. AMA Arch Dermat 74:378, 1956

2 Bras G, Gordon CC, Emmons CW, et al: A case of phycomycosis observed in Jamaica; infection with *Entomophthora coronata*. Amer J Trop Med Hyg 14:141, 1965

3 Martinson FD, Clark BM: Rhinophycomycosis entomophthorae in Nigeria. Amer J Trop Med Hyg 16:40, 1967
4 Cockshott WP, Clark BM, Martinson FD: Upper respiratory infection due to *Entomophthora coronata*. Radiology 90:1016, 1968
5 Ridley DS, Wise MJ: Unusual disseminated infection with a Phycomycete. J Path Bacter 90:675, 1965
6 Williams AO: Pathology of phycomycosis due to Entomophthora and Basidiobolus species. Arch Path 87:13, 1969
7 Pore RS, Goodman NL, Larsh HW: Pathogenic potential of fungal insecticides. Amer Rev Resp Dis 101:627, 1970

Primary Pulmonary Aspergillosis with High Fibrinolytic Activity in the Aortic Intima*

M. E. Pelczar, M.D., Pia Glas-Greenwalt, M.D., and T. Astrup, Ph.D.

Frozen sections of the aorta of a patient with pulmonary aspergillosis were studied for fibrinolytic activity by the histochemical fibrin slide technique. High fibrinolytic activity, caused by a plasminogen activator, was observed along the aortic intima. This unusual observation suggests the existence of a potential for development of fibrinolytic activity in the normal, inactive aortic endothelium of man.

This case report suggests a possible association between pulmonary aspergillosis and an enhanced fibrinolytic activity of the aortic endothelium.

The fibrinolytic activity of tissues is caused by a cellular agent capable of activating a humoral zymogen, plasminogen, to the blood proteinase, plasmin.[1] Assays of this plasminogen activator in extracts of the intima of the human aorta, normal or arteriosclerotic, showed a nearly complete lack of activator,[2,3,4] while the intima of the inferior vena cava was found highly active.[4] Through the use of a histochemical fibrin slide technique, Todd[5] could localize the plasminogen activator to the venous endothelium with little or no activity in the endothelium of systemic arteries, an observation subsequently confirmed by several authors, including ourselves. Noticing unusual fibrinolytic activity in detached endothelium of the arteries of a limb amputated for sarcoma under "bloodless" conditions, Todd[6] suggested that vascular endothelium may have a great fibrinolytic potential, though some stimulus, such as damage, might be required for its release. We report the unexpected finding of a high fibrinolytic activity related to the aortic endothelium of a patient with primary pulmonary aspergillosis.

*From St. Agnes Hospital, Baltimore, and The James F. Mitchell Foundation, Institute for Medical Research, Washton, DC.
Supported by Grant HE-05020 from US Public Health Service, National Institutes of Health, National Heart and Lung Institute.
Reprint requests: Dr. Astrup, Institute for Medical Research, The James F. Mitchell Foundation, 5401 Western Avenue, NW, Washington, D.C. 20015

Case Report

Pertinent clinical data were as follows: A 69-year-old woman was seen at the emergency room because of shortness of breath. Hoarseness had developed three years prior to admission and had gradually become severe. For several months difficulty in swallowing and loss of appetite were noticed, and considerable loss of weight developed. For one month she had complained of shortness of breath and coughing and was treated for congestive heart failure only to have her symptoms worsen. At admission the patient was confused and markedly emaciated. The pulse rate was 90 and irregular. Temperature was 98.9°F (orally) and blood pressure 110/90. Respirations were short and labored. Cyanosis was absent. There were frequent extrasystoles and gallop rhythm. ECG depicted a wandering atrial pacemaker with premature ventricular contractions, left ventricular hypertrophy, and anterior myocardial ischemia. Chest x-ray film showed collapse of the left upper lung with mediastinal shift to the left and infiltrate in the right upper lobe. Hematocrit was 32 percent; hemoglobin, 10.0 gm per 100 ml. White blood count was 7,700/mm^3 with normal differential count. Results of urine analysis were normal. The patient died on the second hospital day.

Pulmonary aspergillosis was diagnosed post mortem with *Aspergillus fumigatus* cultured from abscesses in both lungs. The fungus had invaded the pulmonary parenchyma radially. Dense pleural adhesion and fibrous thickening were found along the posterior aspect of the left lung. A clear, yellow-brown effusion (180 ml) was present in the right pleural cavity. There was moderate atherosclerosis of the coronary arteries and aorta. The weight of the heart was 250 gm. There was mild hypertrophy of the right and left ventricles but no significant dilatation. The myocardium was light brown with cells filled with lipofuscin pigment. The liver showed portal fibrosis and striking deposits of lipochrome pigment in the hepatic cells. Additional autopsy findings were unremarkable.

From a segment of the descending thoracic aorta, refrigerated overnight in saline, samples with grossly normal intima and with moderate atherosclerosis were dissected and frozen in small aluminum containers placed in acetone-dry ice. Sections were cut at 8 μ to 10 μ on a cryostat microtome and collected on precleaned microscope slides. After brief drying in the air, the sections were covered with a mixture of bovine plasminogen-rich fibrinogen and bovine thrombin. The slides were left for 20 minutes in a moist chamber at 10 to 15°C for clot stabilization and then incubated at 37°C for periods ranging from 30 to 90 minutes. Following fixation in formaldehyde, the sections were stained with Harris' alum hematoxylin and mounted with glycerin jelly. Other details were as described before.[7]

Intensive lysis appeared as a clear, ribbon-shaped zone along an apparently intact intimal surface after 30 minutes of incubation, and increased in size with prolonged incubation, and the usual, well-demarcated focal zones of lysis in the adventitia were seen related to intact or torn vascular structures (Fig 1). Sagittal sections or imprints obtained on frozen slides from the fresh luminal surface showed intensive lysis related to endothelial cells. Lysis was absent along intimal surfaces of atheromatous areas, where close examination showed that most of the endothelium had been lost, possibly