The Diagnosis of Fungal Infections of the Respiratory Tract

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ABSTRACT

The diagnosis of histoplasmosis, actinomycosis, candidiasis, nocardiosis, cryptococcosis and aspergillosis are presented.

Introduction

In the past, fungal disease of the lung was regarded by most physicians as a rarity which occurred in very young and very old patients. Only within the last twenty years have large numbers of subclinical infections in otherwise healthy people been appreciated. Physicians' concepts of immunology and knowledge of unpaired delayed hypersensitivity are of even more recent vintage. An increasing number of diseases have been shown to have a demonstrable defect in cellular immunity. These same diseases are those in which fungal disease of the lung may play a decisive factor in the eventual fate of the patient.

Recent technology and a more aggressive approach to illnesses which are not regarded as having primary immunological deficiency have increased the awareness of fungal disease. Of particular importance are the advances in organ transplantation, the widespread use of antibiotics and the application of corticosteroid and immunosuppressive therapy to disease states heretofore regarded as untreatable.

To establish the diagnosis of a fungal infection is a difficult task. Clinically, one must first consider the historical data of the patient with particular reference to a previously diagnosed underlying disease or condition which has left a defect in cellular immunity. Such diseases are well known. Current or antecedent drug therapy which has affected immunological mechanisms is also an important historical factor. Secondly, the physician must consider the patient's exposure to dusts, animal droppings and inorganic vectors which harbor fungal spores and hyphae. Finally, the patient's recent travels in relationship to his clinical illness adds a third dimension to the historical data.

In fungal lung disease, there is usually evidence of a chronic pneumonia both by physical exam and roentgenographically. However, a few specific clues as to etiology can be obtained as it is the rule to see an atypical presentation of such diseases. Fungal infections have no distinguishing features when fever curves, white blood counts, sputum production and character and other biochemical abnormalities are considered. The exception becomes the rule.
and only occasionally will the physician observe a typical skin lesion, a draining sinus or the classical X-ray picture of a specific fungal infection.

In epidemiological surveys and epidemics, fungal skin tests have proved useful, but they are less reliable and unpredictable when one considers a specific patient. Many patients who develop fungal disease cannot respond normally to immunological challenge and as high as 45 percent negative skin tests have been reported in series of known disseminated fungal infections. In many fungal diseases which affect the lungs, a suitable antigen is not available. Serological tests for fungal antibodies are useful diagnostic tools in a number of instances. However, few laboratories are equipped to do such tests. The tests are laborious, results are delayed and the diagnosis often postponed while the physician waits to demonstrate a high titer. Our experience with reference laboratories indicates that if the physician waits for a fungal serology or complement fixation test, he is faced with a dead or seriously ill patient or a wrong diagnosis by the time either a positive or negative report arrives.

The proof that fungal lung disease exists rests with actual demonstration of the organism in lung tissue or repeated recovery of the organism from pulmonary secretions. Occasionally, substantial evidence that fungal disease exists in the lung can be gained from demonstration of the organism in liver or skin biopsy. Less frequently, a positive blood or bone marrow culture can be found.

The experience at Thomas Jefferson University Hospital (TJUH) can be seen in figure 1 and table I. By far the most common fungal isolate is Candida albicans. The number of clinical cases of disease in a hospital population correlates very well with the number of isolations of any given fungus from month to month and year to year. However, fungi are very common organisms in the human body and in the environment, and many contaminants and non-infectious organisms are recovered. Therefore, one must rely heavily on biopsy material when the clinical assessment does not correlate well with culture material.

Of particular interest to pulmonary physicians in the eastern United States are histoplasmosis, actinomycosis, candidiasis, nocardiosis, cryptococcosis, and more recently, aspergillosis. Blastomycosis and coccidioidomycosis are seen only rarely.

Fungal Disorders

Histoplasmosis

Histoplasmosis, a disease which is endemic in the Ohio, Mississippi and St. Lawrence River Valleys, is caused by the organism Histoplasma capsulatum. Humans

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Fungal Infections</th>
<th>Thomas Jefferson University Hospital</th>
<th>Serious Fungal Infections—T.J.U.H.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967</td>
<td>'68</td>
<td>'69</td>
<td>'70</td>
</tr>
<tr>
<td>Candida</td>
<td>7</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>11</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Nocardia</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Histoplasma</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Coccidioides</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
are infected by inhalation of mycelial containing soil after which the organism fruits and eventually resides in cell cytoplasm as a yeast. Positive identification by smears of lung secretions is unusual, but occasionally cultures of sputa or bone marrow are positive. In infected tissue, the organism can be seen as a 3 to 5 μ oval yeast and is best stained by the PAS or silver stains. Clinically, three distinct forms of the disease are described: (1) primary, (2) chronic active and (3) disseminated histoplasmosis. Patients with primary histoplasmosis are often asymptomatic with an abnormal chest X-ray. The disease usually begins with mild respiratory symptoms and fever which can progress to a frank pneumonia accompanied by hilar lymph node enlargement. A calcified nodular lesion may be the sequel to such an infection. Rarely, mediastinal involvement with pericarditis and obstructive lymphadenopathy with fibrosis are more serious complications. With heavy exposure, several foci develop simultaneously and leave multiple calcified nodules in the lung fields, so-called popcorn calcifications.

Chronic active histoplasmosis seen clinically is a chronic pneumonia with systemic symptoms in which the X-ray picture is not unlike that of tuberculosis (figure 2). Cavitlation may occur and resolution is unusual without specific antibiotic therapy. The diagnosis cannot be made without histological confirmation or recovery of the organism from body secretions.

Disseminated histoplasmosis is by far the most virulent form and usually occurs in the immunosuppressed patient. It may resemble miliary tuberculosis and, occasionally, is the sequel to a primary infection. The primary manifestations of the disease are extrapulmonary while the chest X-ray may be normal or resemble the primary or chronic forms of the disease. The diagnosis is confirmed by recovery of the organism from either the bone marrow or a cutaneous ulcer. The skin test is usually negative.

**Actinomycosis**

Actinomycosis, caused primarily by *A. israelii*, presents as a pleural based pneumonia indistinguishable by X-ray from lobar pneumonia caused by the pneumo-
coccus (figures 3 and 4). The organism is of endogenous origin, usually infecting the lungs by aspiration of organisms from the mouth. Occasionally, one can demonstrate fistulous sinus tracts, broncho-pleural fistulas or emphysema. However, confirmation of the diagnosis depends on demonstration of the sulfur granule in empyema fluid or biopsy material and subsequent culture of the organism. Gram stain reveals gram positive, filamentous mycelia which are easily confused with Nocardia. However, Nocardia usually can be demonstrated to be acid-fast.

Candidiasis

Candida albicans, a budding yeast with mycelial forms when invasive, is isolated with rarity as the causative agent in pulmonary secretions in the absence of severe debility, immunosuppression or massive antibiotic therapy. However, in such patients it is a frequent cause of severe bronchitis and bronchopneumonia which clinically and by X-ray is not specific. The diagnosis depends on demonstration of the dimorphic forms in sputum or lung in the absence of other pathogens. Blood cultures are frequently positive and accompanying endocarditis or other evidence of dissemination is not unusual. Unless appropriate antibiotic therapy is given, the disease is frequently fatal.

Nocardiosis

In contrast to Actinomyces, which they closely resemble morphologically, Nocardia species are commonplace in the environment. N. asteroides, the infecting agent in man, is a gram positive branching organism which is often acid fast. Occasionally, sulfur granules are seen but the organism is cultured easily from abscesses and active granulomas. By ordinary histological preparation, the organism is difficult to identify and, even when the silver methenamine stain is done, it cannot be distinguished in tissue from Actinomyces.

Not unlike other fungal infections, nocardiosis presents as a chronic pneumonia,
often with cavitation. Patients with alveolar proteinosis and patients with lymphoma and other reticulo-endothelial disease are particularly susceptible to this disease.\textsuperscript{1} Diagnosis depends on culture evidence of the organism in pus.

**Cryptococcosis**

*Cryptococcus neoformans* is a spherical budding yeast is the infecting agent in this chronic pneumonia. The organism is doubly-refractile in India ink wet mount preparations and easily identified in tissue with PAS or silver stains. Positive sputum cultures are rare\textsuperscript{2}; however, when pulmonary cryptococcosis is accompanied by meningitis or arthritis, a positive wet mount preparation of either spinal fluid or joint fluid for *Cryptococcus* confirms the diagnosis.\textsuperscript{6}

Clinically, there may be no symptoms and often the diagnosis is made at thoracotomy done to remove a pulmonary mass. The infiltrate is more sharply defined by X-ray than other fungal pneumonias and is usually peripheral. Small, thick-walled cavities are occasionally described (figures 5 and 6). Skin tests are not helpful but complement fixation serological titers and latex agglutination tests for antigen, although difficult to obtain, are very specific.\textsuperscript{11}

**Aspergillosis**

Aspergillus species are abundant in nature and are frequent laboratory contaminants (table II and figure 7). Although a number of species are known to cause pulmonary infection, *A. fumigatus* is by far the most common. The organism is detected in the laboratory by saline wet-mount in which branching hyphae and characteristic conidiospores are easily seen. Confirmation of the diagnosis is made by repeated bronchial isolation of the same species, demonstration of precipitating antibodies by double diffusion in agar gel or by identification of the organism in tissue.

Aspergillosis is a growing clinical problem. Three pulmonary varieties are identified: (1) fungus ball, (2) pneumonia with dissemination and (3) allergic bronchopulmonary aspergillosis. In the fungus ball

<table>
<thead>
<tr>
<th>TABLE II</th>
<th>ASPERGILLUS ISOLATIONS - TJUH</th>
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<tbody>
<tr>
<td>1967</td>
<td>139</td>
</tr>
<tr>
<td>1968</td>
<td>240</td>
</tr>
<tr>
<td>1969</td>
<td>119</td>
</tr>
<tr>
<td>1970</td>
<td>202</td>
</tr>
<tr>
<td>1971</td>
<td>239</td>
</tr>
</tbody>
</table>

**Respiratory**

- Pleural - peritoneal 21 (10%)
- SF 18 (8%)
- Blood and BM 12 (6%)
- Skin abscess 11 (5%)
- Unknown 9 (4%)
- Feces 7 (3%)
- Endometrium - cervix 6 (3%)
- Ear and nose 5 (2%)
- Environment 5 (2%)
- Lung 4 (2%)
- Urine 4 (2%)
- Kidney and liver 4 (2%)
- Lymph node 3 (1%)
- boil 1 -
type, the organism invades previously cavi­
tated lung or cystically destroyed lung and
forms the roentgenographically character­
istic intracavity “aspergilloma” (figures 8
and 9). Dense pleural thickening is often
seen accompanying a parenchymal inflam­
atory reaction around the cavity.8 Hemo­
ptysis is the most common symptom.
Identification of the organism in the fungus
ball histologically and by culture, repeated
positive sputum cultures or strongly posi­
tive serum precipitating antibodies all add
credence to the diagnosis. The skin test
with aspergillus antigens is negative.

Disseminated aspergillosis is a pneumatic
process with systemic symptoms accom­
panied by copious amounts of purulent
sputum in which the organisms can be
identified. Specific serum precipitating anti­
bodies are only found in a few instances.
Positive blood cultures and evidence of
spread outside the chest is often present in
these severely ill patients. This form is uni­
versally fatal unless appropriate therapy is
given.

Allergic bronchopulmonary aspergillosis
present clinically as intermittent eosino­
philic pneumonia accompanied by asthma
and peripheral eosinophilia.3 Bronchiec­
tasis has been described. Characteristic red­
brown plugs which contain the organism
are coughed up. The diagnosis is confirmed
by demonstration of both serum precipitat­
ing antibodies, hypersensitivity skin reac­
tions to cutaneous antigens in combination
with isolation of the organism from infected
plugs. Bronchoscopy and corticosteroids are
curative.
Summary

Fungal infections seen in pulmonary disease are a number of overlapping clinical syndromes in which the physician must rely heavily on the microbiological laboratory for specific etiologic diagnosis. Newer techniques of serologic identification and special staining methods in tissue add to the physician's diagnostic capabilities in some instances. Clinical characteristics of the various fungal lung infections with specific methods of diagnosis are discussed. Emphasis is placed on morphological identification of the organism and subsequent cultural recovery of the fungus from body fluids and tissue.

References