Fungal Pneumonia (Part 4)

Invasive Pulmonary Aspergillosis*

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Invasive pulmonary aspergillosis (IPA) is a necrotizing pneumonitis caused by several Aspergillus species. IPA is characterized by hyphal proliferation in the pulmonary parenchyma and by mycotic invasion of the pulmonary vasculature, with resultant hemorrhagic infarction. Aspergillosis is a disease of "medical progress" and is the second most common invasive mycosis in immunocompromised hosts (after Candida).1,8 IPA is a treatable disease that, unfortunately, is often unrecognized antemortem. In this review, emphasis is on certain clinical, radiologic, and laboratory studies that make earlier diagnosis and therapy for IPA potentially possible.

Mycology-Epidemiology

Aspergillus is a ubiquitous soil saprophyte, frequently isolated on settle plates on hospital wards where unfiltered outside air circulates through open windows.8 There is a significant decline in both settle plate Aspergillus counts and cases of nosocomial aspergillosis when mechanical ventilation air filtration systems are introduced in-hospital.4 This suggests that aspergillosis is acquired via airborne spore inhalation. In man aspergillosis most often is due to A fumigatus, A flavus, and A niger.

In special stain microscopy (eg, methenamine-silver stain) of tissue sections from patients with aspergillosis, the fungus consists of broad, septate hyphae (Fig 1) with repeated branching at 45° ("forked stick"), in contrast to the mycelia of Mucor, which are nonseptate and branch at 90° angles.

Pathogenesis of IPA

There have only been 15 documented cases of IPA in normal hosts.5,7 The vast majority of IPA cases occur in patients with hematologic malignancies,5,9 especially during induction or maintenance chemotherapy for acute, nonlymphocytic leukemia. In addition, recipients of renal and

Figure 1. Mycelial phase of Aspergillus fumigatus in lung tissue (silver-methenamine, original magnification × 400).
cardiac transplants\textsuperscript{10,11} are at increased risk for IPA, particularly during episodes of organ rejection, when immunosuppressive therapies are generally intensified. Occasionally, IPA has complicated such diseases as hepatic cirrhosis, miliary tuberculosis, and pulmonary psittacosis.

Patients with IPA usually share the following predisposing factors\textsuperscript{8}: (1) high-dose steroid regimens; (2) cytotoxic chemotherapy, or (3) leukopenia associated with marrow- ablative chemotherapy or myelophthisic marrow replacement (Table 1).

In experimental studies, only corticosteroid therapy has been shown conclusively to augment pulmonary aspergillosis.\textsuperscript{12} In mice first given cortisone acetate, then challenged by aerosolized \textit{A. flavus} the mortality is very high (88 percent in one study). The involved lungs show extensive hemorrhagic bronchopneumonia and hyphal invasion of bronchial walls and arterioles; this is similar to the histopathology seen in human IPA.\textsuperscript{13} Recent studies have suggested that steroids inhibit the fusion of lysosomal membranes of the type II pneumophagocyte with \textit{Aspergillus} spores following ingestion, allowing for intracellular \textit{Aspergillus} germination. The role of cytotoxic chemotherapy in predisposing patients to IPA has been less extensively studied than that of corticosteroids. However, these agents appear to induce two risk factors for aspergillosis: (1) marrow-ablative neutropenia; and (2) erosive mucositis, particularly of the alimentary tract. Of note, IPA in the immunocompromised host has often followed recent infection with \textit{Pseudomonas aeruginosa}.\textsuperscript{9}

The portal of entry for IPA is probably via tracheobronchial aspiration, and nasopharyngeal colonization is believed to be important. Aisner et al\textsuperscript{15} have recently demonstrated that in leukopenic leukemic patients, surveillance nasal cultures posi-

\begin{table}[h]
\centering
\caption{Predisposing Factors in Invasive Pulmonary Aspergillosis (IPA)\textsuperscript{*}}
\begin{tabular}{ll}
\hline
Feature & Mean Percent in Reported Cases of IPA \\
\hline
Concomitant corticosteroid treatment & 94 \\
Cytotoxic chemotherapy & 90 \\
Recent or concurrent broad-spectrum antibiotics & 88 \\
Leukopenia (<1,000 cells/mm\textsuperscript{3}) & 69 \\
Acute leukemia relapse or acute organ transplant rejection & 52 \\
\hline
\end{tabular}
\textsuperscript{*Source: References 8-11, 19, and 31-33.}
\end{table}

\textbf{Figure 2A.} Target lesion of early invasive pulmonary aspergillosis. Thrombosed pulmonary arteriole (arrow) at rim of hemorrhagic and necrotic lesion. (Reproduced with permission of JB Lippincott Co. and Dr. Richard L. Myerowitz).

\textbf{Figure 2B.} Gross macroscopy of lung of patient with invasive pulmonary aspergillosis. Large wedge-shaped infarcts; arrows denote thrombosed pulmonary vessels. (Reproduced with permission of JB Lippincott Co. and Dr. Richard L. Myerowitz).
tive for Aspergillus frequently antedate development of frank IPA or disseminated aspergillosis.

**HISTOPATHOLOGY**

The histopathology of human IPA has been elegantly delineated by Orr et al. On gross macroscopy, the typical early lesions are 1 to 3-cm nodules or target lesions composed of a central yellow-gray zone of tissue necrosis and a surrounding rim of hemorrhage, with a thrombosed artery at the edge of the lesion (Fig 2). These lesions arise via endobronchial hyphal proliferation followed by transbronchial invasion of subjacent pulmonary arterioles, with ischemic necrosis of small areas of the lung. Target lesions are usually present during the first two weeks of the IPA syndrome, progressing abruptly to either diffuse bilateral pulmonary consolidations (with or without cavitation) or, less commonly, to wedge-shaped, pleural-based infiltrates, representing hemorrhagic infarction of major pulmonary arteries. In view of the frequency of pulmonary infarction in the histopathology of IPA, it is somewhat surprising that only a minority of patients with IPA have clinical symptoms or signs of "acute pulmonary infarction."

**EXTRAPULMONARY INVOLVEMENT IN IPA**

In about 10 to 25 percent of patients with IPA, extrapulmonary dissemination is found at autopsy. The organs most frequently involved are the gastrointestinal tract, brain, heart, liver, spleen, kidney, and thyroid.

**CLINICAL FEATURES OF IPA**

Physical findings in IPA are nonspecific, consisting generally of fever and pulmonary rales or rhonchi. Although extrapulmonary aspergillus dissemination occurs in only about 25 percent of patients with IPA, extrapulmonary Aspergillus dissemination may present dramatic clinical syndromes and should be carefully examined for clues to underlying IPA. Mucosal ulceration secondary to hyphal invasion may occur anywhere in the alimentary tract and present as major gastrointestinal hemorrhage. In the classic autopsy study of Young et al describing 98 patients with disseminated aspergillosis, 21 (24 percent) had deep ulcerations of the stomach, small bowel, or colon, which in six cases caused severe bleeding.

The cranial sinuses, middle ear, and mastoid air cells are frequently overlooked sites of Aspergillus involvement. Thus, the clue to an underlying IPA may be rhinocerebral aspergillosis fea-
preserved, despite extensive roentgenographic involvement.\textsuperscript{18}

The chest roentgenogram is abnormal in 75 to 100 percent of patients early in the IPA syndrome.\textsuperscript{18,19} The earliest lesions are single or multiple nodules (corresponding to the histopathologic target lesions; Fig 3). The chest x-ray film then discloses one of three forms of progressive IPA: (1) cavitation of existing nodules (Fig 4); (2) advancement and enlargement of pulmonary nodules to a picture of diffuse bilateral pulmonary consolidation (Fig 5); or (3) abrupt development of large, wedge-shaped, pleural-based lesions, mimicking bland pulmonary infarction (Fig 6). The frequencies of these roentgenographic lesions in IPA are listed in Table 2. The study of Orr et al defined only about 60 percent of these roentgenographic lesions at postmortem examination as caused by Aspergillus; the rest involved either concomitant bacterial or Candida pneumonitis or intrapulmonary hemorrhage. Of diagnostic importance, IPA should be suspected in the febrile immunocompromised host with roentgenographic nodular or cavitary lesions that are unresponsive to treatment with broad-spectrum antimicrobials.\textsuperscript{9} IPA should also be considered in immunocompromised patients in whom the chest roentgenogram picture of acute pulmonary infarction develops without accompanying dyspnea, pleurisy, or hemoptysis.

**Definitive Diagnosis**

Aspergillus has been recovered from sputum in <10 percent of patients with proved IPA, even when specifically sought in perspective studies of deep mycoses in leukemic patients.\textsuperscript{8,10} As noted previously, isolation of Aspergillus from surveillance nasal cultures of immunocompromised patients is significantly correlated with concurrent or subsequent IPA; negative nasal cultures, however, do not preclude the diagnosis of IPA.

To make the definitive diagnosis of IPA, parenchymal invasion of lung tissue must be demonstrated. Thus, bronchial brushings or washings that are culture-positive for Aspergillus can only be interpreted as presumptive evidence of IPA. Burton et al\textsuperscript{10} have suggested that the discovery of mycelial forms of Aspergillus in fresh preparations of sputa or bronchial washings is a valuable clue to IPA. This concept has not been confirmed to date.\textsuperscript{9} In most instances the diagnosis of IPA is made by lung biopsy. Since parenchymal invasion is the sine qua non of IPA, most investigators recom-

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**Table 2—Roentgenographic Abnormalities in Invasive Pulmonary Aspergillosis (IPA)**

<table>
<thead>
<tr>
<th>Roentgenographic Abnormality</th>
<th>Percent Present</th>
</tr>
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<tbody>
<tr>
<td>Segmental or subsegmental consolidations</td>
<td>22</td>
</tr>
<tr>
<td>Patchy infiltrates</td>
<td>21</td>
</tr>
<tr>
<td>Nodular infiltrates</td>
<td>11</td>
</tr>
<tr>
<td>Cavitary lesions</td>
<td>38</td>
</tr>
<tr>
<td>Normal</td>
<td>8</td>
</tr>
</tbody>
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*Summary of 190 reported patients with IPA in whom chest roentgenography is well defined.\textsuperscript{8,11,12}
mend open lung biopsy to obtain adequate tissue for histopathology. Also, open lung biopsy will permit delineation of concomitant pulmonary infection with other pathogens, such as Candida, Pneumocystis, and cytomegalovirus. Methenamine silver and periodic acid-Schiff stains will visualize the organism, whereas hematoxylin-eosin stains do not.

**Serologic Studies in Aspergillosis**

Since IPA (as well as disseminated aspergillosis) is a difficult diagnosis to establish without tissue biopsy, and empiric antifungal chemotherapy may be unwarranted because of potentially severe drug toxicities, much investigation into antibody sero-diagnosis of aspergillosis has been performed. The standard Aspergillus precipitin assay (by gel immunodiffusion), often positive in high titers in allergic bronchopulmonary aspergillosis and pulmonary aspergillomas, in IPA is generally undetectable or present in low titers. Serum precipitins as determined by counterimmunoelectrophoresis (CIE), enzyme-linked immunosorbent (ELISA), and passive hemagglutination assays have been positive in 70 to 80 percent of patients with IPA. However, the specificity and predictive value of single antibody titers using these assays is relatively low. In medical centers caring for large numbers of immunocompromised patients susceptible to IPA, prospective serologic testing for aspergillus antibodies on a serial basis is suggested; this would be most important during times of intensified corticosteroid or cytotoxic chemotherapy for leukemia or cytotoxic augmentation for transplant rejection. In this setting, seroconversion of Aspergillus antibody assays would be an important diagnostic event.

Recently, several groups have examined assays to detect Aspergillus antigenemia. The most promising of these are the radiolimmunoassays of Schafffer et al and Weiner and the detection of Aspergillus-specific galactomannan antigenemia by immunodiffusion or CIE as described by Reiss and Lehmann. At present, these research techniques are not generally available in clinical serology laboratories.

**Therapy for IPA**

Parenteral antifungal therapy is the cornerstone of treatment of IPA. Unfortunately, there is a wide strain-to-strain variability in terms of in vitro sensitivity to amphotericin B; also, there is no standard accepted method for sensitivity testing of this fungus. In general, it appears that most A. fumigatus strains have minimal fungistatic concentrations (MFCs) to amphotericin B within readily achievable serum levels of the drug (0.5 to 1.5 μg/ml); however, A. flavus strains tend to have MFCs above clinically attainable serum amphotericin B levels.

Also, as opposed to pathogenic Candida and Cryptococcus isolates, which are often highly sensitive in vitro to many single antifungal agents (e.g., amphotericin B, miconazole, 5-fluorocytosine), or to synergistic combinations of such agents, Aspergillus isolates tend to be much less sensitive to such regimens. One promising regimen showing in vitro synergy against Aspergillus is the combination of amphotericin B plus rifampin. At the present time, intravenously given amphotericin B (with or without rifampin) appears to be the drug of choice. The optimum duration of amphotericin B therapy is unknown, and the total doses seen in responding patients with IPA have varied between 400 and 3,000 mg.

An important aspect in the management of IPA in immunocompromised patients is to reduce steroid and cytotoxic chemotherapy, as possible.

Thoracotomy with wedge resection is an additional therapeutic maneuver that may be important in patients with recalcitrant or relapsing IPA (despite appropriate medical regimens) and in whom pulmonary lesions are roentgenographically well-defined in a single pulmonary segment.

Holmberg and co-workers recently reported that serial determinations of anti-Aspergillus precipitin antibody titers by ELISA techniques may serve as a useful therapeutic and prognostic serologic marker in patients with histologically confirmed IPA on systemic antifungal therapy. In a study of nine such patients, a serial rise in ELISA titers while patients were receiving antifungal treatment correlated with histologically documented recovery from aspergillosis, whereas those patients with declining or persistently intermediate titers died, and autopsies showed widely disseminated infection.

**Prognosis of IPA**

As in most deep mycoses in immunocompromised hosts, the outcome of IPA is directly correlated with early diagnosis and therapy, induction of remission of the underlying disease, and with reversal of chemotherapy-induced marrow suppression. Of note, the prognosis of IPA in patients with renal and cardiac transplantation appears more favorable than in patients with underlying leukemia. This may relate to the ability to adjust steroid-cytotoxic drug regimens more freely in
organ transplantation than in leukemia in relapse.

The prognosis of IPA still remains grim. However, with the aforementioned newer serologic techniques for earlier diagnosis of IPA and the recent aggressive approaches to lung biopsy in the immunocompromised host with “fever and pulmonary infiltrate” syndromes,16-18 it is hoped that the high morbidity and mortality of IPA will decline. Patients with IPA complicating renal or cardiac transplantation have a relatively lower mortality while receiving antifungal therapy (about 25 percent),10,11,30 as opposed to patients with hematopoietic or lymphoreticular malignancies with IPA (about 70 percent).8,9,10,31

REFERENCES