Invasive Pulmonary Aspergillosis Due to *Aspergillus terreus*: 12-Year Experience and Review of the Literature

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A 12-year retrospective analysis was done to identify and evaluate in detail cases of invasive pulmonary aspergillosis (IPA) caused by *Aspergillus terreus*. We identified 13 *A. terreus* infections among 133 total cases of confirmed invasive aspergillosis; 11 were IPA and 2 were primary peritoneal infections. Of the 11 patients with IPA, 7 developed neutropenia during hospitalization, and the remaining four were receiving immunosuppressive agents. Ten patients with IPA died; one liver transplantation patient without neutropenia survived after treatment with amphotericin B, itraconazole, and a pulmonary lobectomy. Six patients developed disseminated disease, with the heart the most common extrapulmonary site identified (four patients). These cases demonstrate that IPA caused by *A. terreus* rapidly progresses in immunocompromised patients receiving amphotericin B and illustrate the need for sensitive diagnostic tests and more effective antifungal agents.

Invasive aspergillosis is the most common invasive mold infection occurring in immunocompromised patients [1–6]. Primary infection usually involves the respiratory tract following environmental exposure to *Aspergillus* conidia and may, in a severely immunocompromised patient, disseminate to other organs [2, 6–9]. Primary infection of nonpulmonary sites, most commonly affecting the skin or the paranasal sinuses, has been described [10–12]. *Aspergillus fumigatus* and *Aspergillus flavus* are the species most commonly causing invasive mold infections [2–6, 13–15]. The difference in incidence is related to environmental factors that support growth of a particular species [7, 8, 16, 17]. Other species of *Aspergillus*, such as *A. niger* and *A. terreus*, have also been identified as rare causes of invasive disease [5, 6, 13, 14]. Although numerous individual cases of invasive disease caused by *A. terreus* have been described in the past 12 years, no review describing multiple cases at one institution over an extended period of time has been published [18–37]. These reports include a number of isolated cases of localized nonpulmonary infections, such as endophthalmitis, bursitis, endocarditis, and lymphadenitis [19, 21, 24, 27, 31, 35]. Solitary cases of primary invasive pulmonary aspergillosis (IPA) caused by *A. terreus*, with or without dissemination, have also been described [5, 9, 15, 18, 20, 22–24, 26, 28, 32, 33, 35]. Many cases were part of larger studies in which details of the infection were not reported.

Our observations raised the concern that *A. terreus* is associated with higher morbidity and mortality than are other species, which led us to conduct a retrospective 12-year analysis to determine the frequency of IPA caused by *A. terreus* in comparison with that caused by the other species of *Aspergillus*. Overall, 13 cases of invasive aspergillosis caused by *A. terreus* were recognized: 11 primary pulmonary infections and 2 cases of primary peritonitis. The 11 cases of invasive pulmonary disease were further evaluated in detail and the results were compared with those in other published studies from the past 12 years.

Methods

**Cases from the literature.** The English-language literature was searched with use of the MEDLINE databases of the National Library of Medicine. Publications describing IPA caused by *A. terreus*, with or without dissemination, were identified. Infected patients were analyzed by age, sex, underlying disease, primary disease treatment, transplant type (if applicable), site of presenting infection, presence of neutropenia, and organ systems showing histologic evidence of infection.

**Patient population.** Patients were identified by review of the invasive mold disease database established at the University of Nebraska Medical Center (Omaha). The database has information on all patients with invasive mold infection, including those who have undergone bone marrow or liver transplantations at the hospital since 1984 and 1986, respectively. All cases culture positive for *Aspergillus* species during the period from 1 January 1985 through 31 December 1996 were identified from a review of microbiology records. Histopathology and autopsy reports were also reviewed.

**Case definition of invasive aspergillosis.** One or more of the following criteria were used to define cases of invasive aspergillosis: (1) isolation of an *Aspergillus* species from surgical, biopsy, or autopsy specimens (other than specimens from mucosal surfaces) that exhibited histological changes consistent
with those due to invasive *Aspergillus*, (2) isolation of an *Aspergillus* species from a sterile body-site specimen (e.g., an open lung biopsy, brain, bone, or blood specimen) in association with radiographic evidence of disease (e.g., a focal infiltrate, sinusitis, or pleural effusions), and (3) clinical evidence of infection, along with three or more *Aspergillus*-positive cultures of separate specimens from bronchial washings performed over \( \geq 3 \) days. All cases of invasive infection caused by *A. terreus* in this study had histopathologic evidence of tissue invasion. Invasive infections were classified according to the scheme reported by Bodey and Vartivarian [13]. The primary site of infection was the initial source or where the major sign(s) and symptom(s) of disease appeared and were later confirmed as invasive aspergillosis.

**Clinical data.** Clinical information collected about patients with invasive aspergillosis caused by *A. terreus* included the following: clinical evidence of disease (e.g., fever or radiologic changes); underlying illness; transplant type (if applicable); presence of neutropenia (an absolute neutrophil count of \(< 500/\mu L\) ); duration and source of IPA and date of diagnosis; antifungal therapy; and outcome. Autopsy records were also reviewed.

**Statistical analysis.** The difference in percentage of neutropenic patients infected with *A. terreus* vs. *A. fumigatus* was analyzed by the \( \chi^2 \) test with use of MINITAB software, version 11.21 (MINITAB, State College, PA). A \( P \) value of \( > .05 \) was considered not significant.

**Results**

The distribution of *Aspergillus* species causing invasive disease in patients hospitalized at our institution during the study period is shown in table 1. A total of 133 cases of invasive aspergillosis were diagnosed: *A. flavus* was isolated in 67 cases (50.4%), *A. fumigatus* in 51 cases (38.3%), *A. terreus* in 13 cases (9.8%), and *A. niger* (0.8%) and *Aspergillus ustus* (0.8%) in 1 case each. Disseminated disease occurred in 67 cases; 56 of these were considered secondary to primary pulmonary infection. Sites of localized infections were pulmonary (41 cases); cutaneous (12 cases); paranasal sinus, with or without orbital involvement (7 cases); peritoneal (4 cases); and cerebral and auditory (1 case each).

*A. flavus* was the most common cause of disseminated disease (38 cases) as well as of localized involvement in both cutaneous infection (8 cases) and paranasal sinus infection (7 cases). *A. fumigatus* was the most frequent cause of localized pulmonary infection (22 cases), and *A. flavus* was most likely to lead to disseminated disease (38 of 67 cases; 56.7%). Patients with disseminated disease did not survive; 60.7% of patients developed disseminated disease secondary to pulmonary infection diagnosed at postmortem examination.

Comparative data for the three *Aspergillus* species most commonly causing IPA, with or without dissemination, are detailed in table 2. *A. fumigatus* was the most common cause of primary invasive pulmonary disease (43 cases), followed by *A. flavus* (41 cases) and *A. terreus* (11 cases). For patients infected with *A. fumigatus*, the most common underlying condition was liver disease, present in 15 of the 43 cases (34.9%), followed closely by leukemia (13 of 41 cases; 30.2%). In patients infected with *A. flavus*, lymphoma was the most common underlying disease (12 of 41 cases; 29.3%), while *A. terreus* was the most frequent cause of IPA in patients with leukemia (6 of 11; 54.5%).

Neutropenia was present in 63.6% of patients infected with *A. terreus* (median duration of neutropenia, 27 days; range, 6–42 days) (table 2); this duration was followed by that of neutropenia in infections due to *A. fumigatus* (median, 21 days; range, 6–34 days) and *A. flavus* (median, 20 days; range, 15–87 days). The overall survival among patients with IPA with or without dissemination was 7.3% for that due to *A. flavus*,

### Table 1. Overall distribution of *Aspergillus* species causing invasive disease at the University of Nebraska Medical Center, 1985–1996.

<table>
<thead>
<tr>
<th>Disease category</th>
<th>( A. ) flavus</th>
<th>( A. ) fumigatus</th>
<th>( A. ) terreus</th>
<th>( A. ) niger</th>
<th>( A. ) ustus</th>
<th>Total (%)</th>
<th>No. (%) of cases diagnosed postmortem*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>12</td>
<td>22</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>41</td>
<td>10/31 (32.3)</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>0/2</td>
</tr>
<tr>
<td>Paranasal sinus</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0/2</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0/1</td>
</tr>
<tr>
<td>Cerebral</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0/1</td>
</tr>
<tr>
<td>Auditory</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0/0</td>
</tr>
<tr>
<td>Disseminated, secondary to</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>29</td>
<td>21</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>56</td>
<td>34/56 (60.7)</td>
</tr>
<tr>
<td>Nonpulmonary</td>
<td>9</td>
<td>1</td>
<td>1*</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>4/11 (36.4)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>67 (50.4)</td>
<td>51 (38.3)</td>
<td>13 (9.8)</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>133</td>
<td>48/104 (46.2)</td>
</tr>
</tbody>
</table>

* No. of cases diagnosed at postmortem examination per total no. of patients who died.

* Primary peritonitis that ultimately disseminated to the heart, small intestine, pancreas, stomach, and left pleura.
Comparative data from cases due to the Aspergillus species most commonly causing primary invasive pulmonary aspergillosis.

<table>
<thead>
<tr>
<th>Species, underlying condition</th>
<th>Total no. of cases</th>
<th>Median duration of neutropenia in d (range)</th>
<th>No. (%) cases diagnosed during hospitalization</th>
<th>No. (%) of cases diagnosed postmortem*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. fumigatus</td>
<td>43</td>
<td>16 (37.2)²</td>
<td>21 (6–34)</td>
<td>6 (14.0)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. flavus</td>
<td>41</td>
<td>23 (56.1)²</td>
<td>20 (15–87)</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. terreus</td>
<td>11</td>
<td>7 (63.6)²</td>
<td>27 (6–42)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Absolute neutrophil count, <500/µL.

¹ Number of cases diagnosed at postmortem examination per total number of patients who died.
² In statistical analysis of percentages of neutropenic patients infected with A. fumigatus vs. A. terreus, P = .125.

9.1% for that due to A. terreus, and 14.0% for that due to A. fumigatus. For 45.9%–60% of patients who died, the first identification of aspergillosis was made at postmortem examination.

A comparison of diseases caused by A. terreus was made through tabulation of data from 19 cases in the literature and five additional recent cases at our institution (table 3). Ten patients were female, 13 were male, and the sex of one was not reported. The median age was 41 years (range, 1–80 years). The most common underlying disease was leukemia, in 10 patients, all of whom received high-dose chemotherapy and five of whom underwent allogeneic bone marrow transplantation. The next most common underlying condition was liver disease (three patients, all of whom underwent liver transplantation). Overall, 13 of the 21 patients for whom information was recorded became neutropenic during the hospitalization when aspergillosis occurred.

Eleven patients overall had invasive disease localized to the lungs only; the original diagnosis for these patients most frequently was made following a lung biopsy (eight cases) (table 3). All three cases diagnosed by culture of a bronchial washing specimen were subsequently confirmed by histologic examination of lung tissue. Thirteen patients had primary IPA, which ultimately disseminated to extrapulmonary sites. All patients whose disseminated disease originated from a nonpulmonary site (patients 17, 22, and 23) or multiple sites detected in postmortem examination (patients 16, 18, 20, 21, and 24) had abnormal chest radiographs prior to diagnosis of aspergillosis, suggesting the respiratory tract was the initial site of infection. IPA was found upon histological examination of lung tissue at autopsy, a finding confirming this interpretation.

Eight patients in the literature and 7 of the 11 patients at our institution received intravenous amphotericin B (for 5 patients in the literature this information was not reported). The four patients at our institution who did not receive amphotericin B (patients 10, 11, 20, and 24) had aspergillosis diagnosed at postmortem examination. Overall, there were three survivors (patients 1, 6, and 8); all had localized pulmonary infection and received therapeutic doses of amphotericin B (>1,500 mg), and two were treated with itraconazole. One patient at our institution who was not neutropenic (patient 8) also underwent a pulmonary lobectomy of the infected lung.

A postmortem examination was performed in 5 of the 6 cases of disseminated disease at our institution and in 6 of the 7 cases reported in the literature. The most common extrapulmonary site of infection per histologic evidence was the heart (8 patients, including 4 at our medical center) (table 3); the brain and spleen were the second most common, at 5 patients each.

Discussion

This study was conducted to identify published cases of IPA caused by A. terreus and to compare these with cases occurring at our institution. A retrospective analysis of patients with invasive aspergillosis diagnosed at the University of Nebraska Medical Center revealed that A. terreus was responsible for 13 of 133 cases of invasive aspergillosis (9.8%); 11 primarily involved the pulmonary system and 2 involved the peritoneal cavity (table 1). This frequency of A. terreus in our series is comparable with that reported in retrospective studies by Walmsley et al., where 3 of 24 isolates (12.5%) were A. terreus; by Wald et al., where 9 of 133 isolates (6.8%) from bone marrow transplantation patients were A. terreus; and by Khoo and Denning, where 3 of 87 isolates (3.4%) causing invasive aspergillosis in patients with AIDS were A. terreus [4, 6, 15]. The overall rate of primary pulmonary infections (due to any Aspergillus species) in our study was 72.9% (97 of 133 cases), and primary cutaneous infection was the second most common source (12 cases).

Eight of the 11 patients at our institution with IPA caused by A. terreus had hematologic malignancies: 6 had leukemia, and 2 had lymphoma (table 2). All of these patients underwent aggressive chemotherapy and became neutropenic at some time during hospitalization (table 3). This association of A. terreus infection with leukemia had been shown by other investigators; Chang and King [18], as well as Moore et al. [28], each described patients with leukemia who received chemotherapy but did not undergo bone marrow transplantation [18, 28]. Goldberg et al. described a case of invasive disease caused by...
Invasive Aspergillosis Due to *A. terreus*

### Table 3. Clinical characteristics of 24 patients with primary pulmonary invasive aspergillosis, with or without dissemination, caused by *Aspergillus terreus* (including those previously reported in the English-language literature during the period 1985–1996).

<table>
<thead>
<tr>
<th>Infection classification, patient no. [reference]</th>
<th>Age (y) / sex</th>
<th>Underlying disease</th>
<th>Neutropenia (absolute neutrophil count, &lt;500/µL)</th>
<th>Transplant</th>
<th>Original culture-positive specimen from symptomatic patient</th>
<th>Site(s) of histologically evident infection</th>
<th>Antifungal therapy (nontopical)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localized pulmonary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 [18]</td>
<td>60/M</td>
<td>AML</td>
<td>Yes</td>
<td>None*</td>
<td>Bronchial wash</td>
<td>Lung</td>
<td>AmB</td>
<td>Survival</td>
</tr>
<tr>
<td>2 [28]</td>
<td>70/F</td>
<td>CLL</td>
<td>Yes</td>
<td>None*</td>
<td>Lung</td>
<td>Lung</td>
<td>AmB</td>
<td>Death</td>
</tr>
<tr>
<td>3 [26]</td>
<td>37/F</td>
<td>SLE</td>
<td>No</td>
<td>None</td>
<td>Lung</td>
<td>Lung</td>
<td>NR</td>
<td>Death</td>
</tr>
<tr>
<td>4 [5]</td>
<td>46/M</td>
<td>AIDS</td>
<td>No</td>
<td>None</td>
<td>Lung</td>
<td>Lung</td>
<td>NR</td>
<td>Death</td>
</tr>
<tr>
<td>5 [32]</td>
<td>41/M</td>
<td>AIDS</td>
<td>Yes</td>
<td>None</td>
<td>Bronchial wash</td>
<td>Lung</td>
<td>NR</td>
<td>Death</td>
</tr>
<tr>
<td>6 [22]</td>
<td>21/M</td>
<td>ALL</td>
<td>Yes</td>
<td>Allogeneic BM*</td>
<td>Bronchial wash</td>
<td>Lung</td>
<td>AmB, Itr, Mic</td>
<td>Survival</td>
</tr>
<tr>
<td>7 [33]</td>
<td>40/F</td>
<td>CML</td>
<td>Yes</td>
<td>Allogeneic BM-U*</td>
<td>Lung</td>
<td>Lung</td>
<td>AmB</td>
<td>Death</td>
</tr>
<tr>
<td>8 [33]</td>
<td>57/M</td>
<td>HCV</td>
<td>No</td>
<td>Liver</td>
<td>Lung</td>
<td>Lung</td>
<td>NR</td>
<td>Death</td>
</tr>
<tr>
<td>9 [PR]</td>
<td>34/F</td>
<td>NHL</td>
<td>Yes</td>
<td>Allogeneic BM-U*</td>
<td>Lung</td>
<td>Lung</td>
<td>AmB</td>
<td>Death</td>
</tr>
<tr>
<td>10 [PR]</td>
<td>72/M</td>
<td>AML</td>
<td>Yes</td>
<td>None*</td>
<td>Lung</td>
<td>Lung</td>
<td>None</td>
<td>Death</td>
</tr>
<tr>
<td>11 [PR]</td>
<td>46/F</td>
<td>CHB</td>
<td>No</td>
<td>Liver</td>
<td>Lung</td>
<td>Lung</td>
<td>Flu</td>
<td>Death</td>
</tr>
<tr>
<td><strong>Disseminated</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 [23]</td>
<td>80/F</td>
<td>IT</td>
<td>No</td>
<td>None</td>
<td>Bronchial wash</td>
<td>Diaphragm, lung, stomach, heart</td>
<td>AmB, Ket</td>
<td>Death</td>
</tr>
<tr>
<td>13 [23]</td>
<td>28/M</td>
<td>MD</td>
<td>Yes</td>
<td>Allogeneic BM*</td>
<td>Pleural fluid</td>
<td>Brain, heart, liver, spleen, lung, thyroid</td>
<td>AmB</td>
<td>Death</td>
</tr>
<tr>
<td>14 [35]</td>
<td>58/F</td>
<td>AS</td>
<td>No</td>
<td>None</td>
<td>Sputum</td>
<td>Brain, heart, lung, kidney, spleen, thyroid</td>
<td>NR</td>
<td>Death</td>
</tr>
<tr>
<td>15 [24]</td>
<td>65/F</td>
<td>CLL</td>
<td>NR</td>
<td>NR*</td>
<td>Bronchial wash</td>
<td>Brain, heart, adrenal gland, eye, esophagus, lung thyroid, skin</td>
<td>AmB</td>
<td>Death</td>
</tr>
<tr>
<td>16 [15]</td>
<td>2/F</td>
<td>AA</td>
<td>Yes</td>
<td>BM*</td>
<td>Multiple</td>
<td>Lung, skin</td>
<td>AmB, 5-FC</td>
<td>Death</td>
</tr>
<tr>
<td>18 [20]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Multiple</td>
<td>Brain, lung</td>
<td>NR</td>
<td>Death</td>
</tr>
<tr>
<td>20 [9]</td>
<td>23/M</td>
<td>ALL</td>
<td>Yes</td>
<td>Allogeneic BM-R*</td>
<td>Multiple</td>
<td>Adrenal gland, heart, lung</td>
<td>None</td>
<td>Death</td>
</tr>
<tr>
<td>21 [9]</td>
<td>27/M</td>
<td>CML</td>
<td>Yes</td>
<td>Allogeneic BM-R*</td>
<td>Multiple</td>
<td>Heart, lung</td>
<td>AmB</td>
<td>Death</td>
</tr>
<tr>
<td>22 [9]</td>
<td>41/M</td>
<td>AML</td>
<td>No</td>
<td>Allogeneic BM-R*</td>
<td>Brain</td>
<td>Brain, heart, kidney, GI tract, liver, lung, skin</td>
<td>AmB</td>
<td>Death</td>
</tr>
<tr>
<td>23 [PR]</td>
<td>76/M</td>
<td>AML</td>
<td>Yes</td>
<td>None*</td>
<td>Skin</td>
<td>Lung, skin</td>
<td>AmB</td>
<td>Death</td>
</tr>
<tr>
<td>24 [PR]</td>
<td>1/M</td>
<td>SBS</td>
<td>No</td>
<td>Liver/small bowel</td>
<td>Multiple</td>
<td>Heart, kidney, spleen, lung</td>
<td>Flu</td>
<td>Death</td>
</tr>
</tbody>
</table>

**NOTE.**  
AA = aplastic anemia; AG = agranulocytosis of unknown origin; ALL = acute lymphoblastic leukemia; AmB = amphotericin B; AML = acute myelogenous leukemia; AS = acute stenosis; BM = bone marrow; BM-R = bone marrow, related; BM-U = bone marrow, unrelated; CHB = chronic hepatitis B; CLL = chronic lymphoblastic leukemia; CML = chronic myelogenous leukemia; 5-FC = fluocytosine; Flu = fluconazole; GI = gastrointestinal; HCV = hepatitis C virus infection; IT = idiopathic thrombocytopenia; Itr = itraconazole; Ket = ketoconazole; MD = myelodysplasia; Ms = miconazole; NHL = non-Hodgkin’s lymphoma; NR = not reported; PR = present report; PSC = peripheral stem cell; SBS = small-bowel syndrome; TCD = T cell deficiency.  
* This patient received high-dose chemotherapy treatment.  
† This patient was included in the database for patients with invasive mold infections hospitalized at the University of Nebraska Medical Center.  
‡ Aspergillosis diagnosed following postmortem examination.  
§ Patient admitted for brain abscess 247 days after allogeneic bone marrow transplant.
*A. terreus* in a patient with acute lymphoblastic leukemia who underwent allogeneic bone marrow transplantation [22]. In four of our six patients with leukemia, allogeneic bone marrow transplantsations were performed. Opportunistic fungal infections are more common under these circumstances because of the high level of immunosuppression [1, 2, 5, 6].

Two patients at our institution with non-Hodgkin’s lymphoma developed IPA; both (patients 9 and 19) underwent autologous stem cell rescues following treatment with high-dose chemotherapy (table 3). A number of similarities in the clinical courses of these two lymphoma patients were noted, including the initiation of amphotericin B therapy following detection of chest radiographic abnormalities 16–17 days post-admission; the diagnosis of IPA was confirmed 41 and 53 days postadmission, respectively. It is interesting that one patient (number 19) developed disseminated aspergillosis despite receiving 2,430 mg of amphotericin B, whereas the second patient (number 9) had disease that remained localized to the lung and received 1,276 mg of amphotericin B but died.

The three remaining patients with *A. terreus* infection at our institution had liver disease as an underlying condition (patients 8, 11, and 24). Fungal infections are a common complication following liver transplantation, with a reported incidence ranging from 7% to 42% [38]. Even though a majority of fungal infections in these patients are caused by *Candida* species, ~20% are due to *Aspergillus*, with *A. fumigatus* and *A. flavus* causing a majority of these infections. No detailed studies describing *A. terreus* as a cause of invasive aspergillosis in liver transplant patients have been reported. Likewise, *A. terreus* as a cause of infection in lung and heart/lung transplant recipients has also not been reported, suggesting that patients undergoing solid-organ transplantation are at low risk for infection caused by *A. terreus* [39]. Two patients in our study (patients 8 and 11) had aspergillosis confined to the lungs, while patient 24 had disseminated disease involving multiple organs (table 3). For both patient 11 and patient 24, the diagnosis was made following portmortem examination.

Neutropenia is considered a major risk factor for the development of invasive aspergillosis [2, 6, 17]. This was especially evident in patients at our institution, where 63.6% (seven) of 11 patients with neutropenia developed *A. terreus* infections during hospitalization, with a median neutropenia duration of 27 days (range, 6–42 days) (table 2). In comparison, *A. fumigatus* was isolated from 16 of 43 neutropenic patients developing IPA. This difference in percentage of *A. terreus* and *A. fumigatus* infections among neutropenic patients was not statistically significant (*P* = .125). The lack of significance is due in part to the small number of *A. terreus* infections analyzed, but the results suggest *A. terreus* may require a higher degree of immunosuppression before infection can occur.

Even though it is well known that the mortality associated with IPA is high, to our knowledge, there have been no studies comparing mortality rates associated with the various species of *Aspergillus* [3, 6]. The survival rate for patients with IPA caused by *A. flavus* was 7.3%, followed by 9.1% for *A. terreus* IPA and 14.0% for *A. fumigatus* IPA, with a combined survival of 10.5%. The ineffectiveness of amphotericin B in the treatment of aspergillosis has been shown numerous times and is again reflected in this study [2, 40]. Of the patients in this collected review, only three survived with IPA, and all had localized pulmonary infection.

The surviving patient at our institution (patient 8) was not neutropenic and received therapy with both amphotericin B and itraconazole. In addition, aggressive surgical intervention was utilized for this patient, including lobectomy of the infected lung. Robinson et al. have suggested that pulmonary resection be performed for IPA in immunocompromised patients to increase chances of survival [33]. Patient 1, another survivor, was neutropenic and received amphotericin B. The remaining survivor (patient 7) received both amphotericin B and itraconazole. Itraconazole has shown some effectiveness in the treatment of aspergillosis, but the response rates are considered no better than those reported for amphotericin B [41]. In in vitro studies, *A. terreus* was markedly more susceptible to itraconazole than to amphotericin B, suggesting that this antifungal should be considered when *A. terreus* is causing invasive infection [42].

Extrapulmonary spread of *A. terreus* was noted in six of our patients; dissemination to the heart was most common (four patients) (table 3). In a previous study at our institution of infection caused by all species of *Aspergillus*, the brain was recognized as the most common site of dissemination [3]. In four of the seven cases reported in the literature of disseminated aspergillosis caused by *A. terreus*, dissemination to the heart was also recognized [23, 24, 35].

Improved methods for the timely isolation and identification of the causative agent of aspergillosis are clearly needed. The ability to distinguish *A. terreus* from other species may be important from an epidemiological standpoint, and as this study suggests, it may also be important from both therapeutic and prognostic standpoints [8, 43]. Even though amphotericin B is considered the antifungal of choice for treatment of IPA, treatment with this antifungal is still associated with an extremely high mortality [3, 6, 40].

Our report suggests that surgical intervention, as well as combined therapy with amphotericin B and itraconazole for patients with IPA caused by *A. terreus*, may be a treatment option to consider. Additional studies are needed to evaluate whether newly available preparations of amphotericin B combined with itraconazole offer a therapeutic advantage over existing treatments for *A. terreus* infection [44].

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References


