Invasive Aspergillosis Due to *Neosartorya udagawae*


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**Background.** Invasive aspergillosis (IA) is most commonly caused by the morphospecies *Aspergillus fumigatus*. However, genetic-based methods indicate that organisms phenotypically identified as *A. fumigatus* actually constitute a mold complex, designated *Aspergillus* section *fumigati* subgenus *fumigati*.

**Methods.** Multilocus sequencing and analysis was performed on fungi identified as *A. fumigatus* from the clinical culture collection maintained at the National Institutes of Health from 2000 through 2008, with a focus on the internal transcribed spacer 1 and 2 regions of ribosomal DNA (rDNA), β-tubulin, and rodlet A genes. We reviewed the medical records, radiology, and histopathology of corresponding patients. To confirm identification of *Neosartorya udagawae* isolates, mating studies were performed with reference strains. Antifungal susceptibility testing was performed by broth microdilution and read at 48 hours.

**Results.** Thirty-six cases of infection attributed to *A. fumigatus* were identified; 4 were caused by *N. udagawae* (3 in patients with chronic granulomatous disease and 1 in a patient with myelodysplastic syndrome). Disease due to *N. udagawae* was chronic, with a median duration of 35 weeks, compared with a median duration of 5.5 weeks for patients with chronic granulomatous disease who had infection due to *A. fumigatus sensu stricto* (P < .05, Mann-Whitney U test). Infection spread across anatomical planes in a contiguous manner and was refractory to standard therapy. Two of the 4 patients died. *N. udagawae* demonstrated relatively higher minimum inhibitory concentrations to various agents, compared with those demonstrated by contemporary *A. fumigatus sensu stricto* isolates.

**Conclusions.** To our knowledge, this is the first report documenting infection due to *N. udagawae*. Clinical manifestations were distinct from those of typical IA. *Fumigati*-mimetics with inherent potential for antifungal resistance are agents of IA. Genetic identification of molds should be considered for unusual or refractory IA.

Invasive aspergillosis (IA) affects 5%–20% of patients with hematological malignancies and transplants [1–3]. Overall mortality rates range from 30% to 60% [4–7]. Most mold-attributable deaths occur within the first 6 weeks of treatment [8]. Among primary immunodeficiencies, chronic granulomatous disease (CGD) patients are uniquely susceptible to IA, with 25%–35% of these patients affected [9, 10]. Therefore, CGD provides an opportunity to study this infection within the context of a fixed immunological deficit.

Refractory IA, which has been defined as disease progression or failure to clinically improve after ≥7 days of standard therapy [11, 12], may be a function of underlying disease, concomitant iatrogenic immunosuppression, or pharmacokinetics. Pathogen-related factors are poorly understood. Drug susceptibility is inferred from speciation. Most isolates of *Aspergillus fumigatus* are considered to be sensitive to amphotericin B (AmB), extended-spectrum triazoles, and caspofungin [12].

IA is most commonly caused by *A. fumigatus*, a morphospecies identification based on phenotype of colonies and spore-bearing structures. However, organisms previously recognized as *A. fumigatus* now constitute a complex that is designated *Aspergillus*...
section *fumigati* subgenus *fumigati*. Within this group are asexual members (anamorphs, termed *Aspergillus*), some of which may also have sexual forms (teleomorphs, termed *Neosartorya*). Anamorphic human pathogens include *A. fumigatus* sensu stricto and *Aspergillus lentulus*, while pathogenic teleomorphs include *Neosartorya pseudofischeri*, *Neosartorya fischeri*, and *Neosartorya hiratsukae*. Although these organisms display the characteristic microscopic morphology of *A. fumigatus* in vitro, they may behave differently. Thus, the clinical relevance of subspeciation remains unclear.

*Neosartorya udagawae*, which resembles *A. fumigatus*, was originally identified from Brazilian soil [13]. Its anamorph, *Aspergillus udagawae*, has been identified among clinical culture collections, although disease was not documented [14]. We describe *N. udagawae* that caused disease distinct from typical IA.

**METHODS**

**Case identification.** The National Institutes of Health clinical microbiology database for the period 2000–2008 was reviewed for molds that fulfilled the following criteria: (1) the mold was a filamentous fungus resembling or reported as *A. fumigatus*, (2) the source of the isolate was a significant clinical specimen (e.g., tissue and sterile sources), and (3) sequence-based identification (see below) was performed on the isolate. The respective patients were identified and their medical records, computed tomographs, and histopathology were reviewed. The estimated duration of IA was defined as the time from documentation of first symptom of infection (or first radiographic evidence if asymptomatic) to death from infection or control of disease. Control of disease was defined as the earliest date of radiologic improvement or stabilization associated with resolution of clinical symptoms [15].

**Morphological identification.** Isolates were identified on the basis of colony features and morphology under light microscopy by means of routine clinical mycology laboratory media and incubation conditions.

**Genetic identification.** Isolates were identified by multilocus sequence analysis of the internal transcribed spacer 1 and 2 regions flanking 5.8S ribosomal DNA (rDNA) (ITS1–5.8S–ITS2), (partial) β-tubulin gene (*bna*), and (partial) rodlet A gene (*rodA*), as described elsewhere [16–18]. Briefly, each isolate was subcultured onto Sabouraud dextrose agar at 37°C for 5 days. Mycelial DNA was extracted using the UltraClean Microbial DNA Isolation kit, according to manufacturer’s modifications for molds (MoBio Laboratories). Polymerase chain reaction was followed by amplicon purification with the Microcon YM-100 centrifugation filter device (Millipore). Sequencing was performed on the 3100 sequencer (Applied Biosystems), analyzed using Lasergene software (DNASTAR), and compared with GenBank sequences by means of nucleotide Basic Local Alignment Search Tool (BLASTn). Multiple-sequence alignment was performed with CLUSTAL W, and percent similarity was calculated.

**Strains.** The type strains of heterothallic *N. udagawae* from Centraalbureau voor Schimmelcultures (CBS; 114217 and 114218) are environmental strains that represent 2 opposite mating types. The 4 clinical isolates and the reference strains were grown on malt or oatmeal agar plates at room temperature for 7 days. Conidia were harvested in phosphate-buffered saline with polysorbate surfactant (Tween) at a concentration of 0.01% and washed with ultrapure water. The *A. fumigatus* clinical strain, B-5233, was cultured as described elsewhere [19]. For morphological studies, conidia were inoculated onto thin layers of malt agar, incubated for 3–7 days at 37°C, and visualized by light microscopy with lactophenol cotton blue.

**Mating studies.** To confirm genetic-based identification, mating studies were performed between each clinical isolate and the reference strains on oatmeal agar incubated at 25°C in the dark for ≥6 weeks [20].

**Antifungal susceptibility testing.** Broth microdilution was performed at the Fungus Testing Laboratory, University of Texas Health Sciences Center, according to guidelines from the Clinical and Laboratory Standards Institute [21]. Minimum inhibitory concentrations (MICs) at 48 hours were reported for AmB, itraconazole, voriconazole, posaconazole, and terbinafine. Minimum effective concentrations at 48 hours were reported for caspofungin and micafungin.

**CLINICAL CASES**

**Patient 1.** A 27-year-old man with X-linked CGD presented with cough and hemoptysis. A left lower-lobe nodule yielded a mold morphologically identified as *A. fumigatus*. AmB and voriconazole led to some symptomatic improvement. AmB treatment was discontinued. He was discharged with a regimen of voriconazole, but cough and hemoptysis recurred.

He had had recurrent cases of pneumonia with *Aspergillus* (no species documented), each apparently successfully treated with AmB. When he was 16 years old, progressive disease with *Aspergillus nidulans* required partial lobectomy, thoracoplasty, and vertebral resection with rod placement. In his 20s, he developed cases of pneumonia with *Paecilomyces* species, *Pseudallescheria boydii*, and *Burkholderia cepacia* complex; all resolved with therapy.

Computed tomography at admission showed multiple left lower-lung nodules. Aspirate yielded *A. fumigatus* (subsequently identified as *N. udagawae*). Treatment was modified to voriconazole and caspofungin. Progression over 2 weeks prompted a change to posaconazole. Two weeks later, new and increasing foci compelled a change to AmB. After 2 weeks, a mixed radiological response resulted in the addition of caspofungin. Clinical and radiological stability was achieved 5.5
months after disease onset. One month later, improvement in the consolidations continued.

**Patient 2.** A 36-year-old woman with CGD presented with nonproductive cough and dyspnea. Computed tomography demonstrated lingular infiltrate with a small cavity. Biopsy was not diagnostic. Broad-spectrum antibiotics and itraconazole (400 mg intravenous daily) were started. One week later, she developed mediastinal lymphadenopathy with left pleural-based thickening. During the ensuing 6 weeks, she slowly became better without significant radiologic improvement. She was discharged with a regimen of itraconazole (400 mg orally daily). After 2.5 months, the dosage of itraconazole was reduced by half for nausea. Two weeks later, productive cough, worsened lingular consolidation, scattered nodules, and persistent mediastinal lymphadenopathy prompted lung biopsies that yielded *A. fumigatus* (subsequently *N. udagawae*). Voriconazole was initiated, but elevated hepatic transaminases prompted a change to posaconazole 10 days later. After 7 weeks, there was significant clinical improvement, normalization of inflammatory markers, and radiologic regression. She completed 7 months of posaconazole without complications.

**Patient 3.** A 33-year-old man with an undefined immu-
nodeficiency presented with fever and pancytopenia. Disseminated histoplasmosis failed to improve after 3 weeks of liposomal AmB, and he was transferred to the National Institutes of Health. Further investigation showed diffuse pulmonary interstitial thickening, infiltrates in the left pulmonary apex and right lower lobe, and disseminated *Mycobacterium avium* complex. Posaconazole, antimycobacterial therapy, and interferon-γ eventually resolved both infections. During his illness, bone marrow analyses showed a myelodysplastic syndrome associated with monosomy 7. While in the hospital and receiving posaconazole, he developed worsening left apical consolidation. Biopsy grew *A. fumigatus* (subsequently *N. udagawae*). Treatment with voriconazole and caspofungin was begun. During the ensuing 11 months, despite several modifications in antimycotics, the apical consolidation expanded, involving the pleura, lingula, fissure, and left lower lobe, accompanied by mediastinal and hilar lymphadenopathy. The right lung demonstrated fluctuating improvement in the lower-lobe consolidation but developed new lesions involving the major fissure, right middle lobe, and apex and a recalcitrant pleural effusion. One year into hospitalization, new fevers with worsening infiltrates led to isolation of *N. udagawae* from bronchoalveolar lavage. Thyroid lesions were observed. Neurological deficits and bilateral cerebral hypodensities led to a biopsy which showed...
Acute branching septated hyphae, although cultures yielded no organism. AmB, terbinafine, and flucytosine were added. Steroids were required for brain edema. The patient expired 5 days later. At autopsy, septated bulbous hyphae were identified diffusely in the lungs (figure 1A) with multiple pleural adhesions, in the left ventricular and septal myocardium with fibrinous pericardium along the tricuspid valve, in both thyroid lobes, and in the brain.

**Patient 4.** A 29-year-old man with X-linked CGD was referred for progressive aspergillosis. He had had recurrent cases of pneumonia with a mold identified as *A. fumigatus* over a protracted course, despite treatment with itraconazole and AmB, wedge resection of the right upper lobe, and multiple pleural adhesions, in the left ventricular and septal myocardium with fibrinous pericardium along the tricuspid valve, in both thyroid lobes, and in the brain.

**Table 1. Characteristics of patients and clinical features of disease due to Neosartorya udagawae.**

<table>
<thead>
<tr>
<th>Patient identifier</th>
<th>Age in years, sex</th>
<th>Year</th>
<th>Underlying disease</th>
<th>Primary site of infection</th>
<th>Subsequent sites of involvement</th>
<th>Estimated duration of illness</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27, M</td>
<td>2004</td>
<td>CGD (gp91phox)</td>
<td>Left lower lobe</td>
<td>Expansion of primary infiltrate with multiple new areas in left lung; subcarinal lymphadenopathy</td>
<td>~26 weeks</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>36, F</td>
<td>2002</td>
<td>CGD (p47phox)</td>
<td>Lingula</td>
<td>Worsening consolidation in lingula and left lower lobe; left pleural-based thickening; mediastinal lymphadenopathy</td>
<td>~26.5 weeks</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>33, M</td>
<td>2006</td>
<td>Myelodysplastic syndrome</td>
<td>Left upper lobe</td>
<td>Expansion of primary infiltrate, left pleura, lingula, left lower lobe; mediastinal and hilar lymphadenopathy; right lung; myocardium and valves; thyroid; brain</td>
<td>~44 weeks</td>
<td>Deceased</td>
</tr>
<tr>
<td>4</td>
<td>29, M</td>
<td>2008</td>
<td>CGD (gp91phox)</td>
<td>Right upper lobe</td>
<td>Progression of primary lesion; mediastinal lymphadenopathy; left lung; right anterior chest wall; liver; mesenteric lymphadenopathy</td>
<td>Possibly 14 years</td>
<td>Deceased</td>
</tr>
</tbody>
</table>

**NOTE.** CGD, chronic granulomatous disease.

RESULTS

From 2000 through 2008, 36 cases of invasive *A. fumigatus* that fulfilled inclusion criteria were identified at the National Institutes of Health: 15 patients had CGD, 5 had leukemia and/or lymphoma, 5 had cancer, 3 had autosomal-dominant hyperimmunoglobulin-E syndrome, and 8 had other illnesses. Sources were pulmonary and/or pleural in 33 cases and extrathoracic in 3 cases.

There were 4 infections with *N. udagawae* that was identified by multilocus sequence analysis, which accounted for 11% of our IA cases (table 1). Three patients had CGD, and 1 patient had an undefined immunodeficiency with myelodysplastic syndrome. The estimated duration of infection in these patients ranged from 26 to 728 weeks (mean, 206.1 weeks; median, 35.25 weeks). Since the majority of *N. udagawae* cases involved CGD patients, a comparator group was identified consisting of all CGD cases within the same time period from which *A. fumigatus* sensu stricto by multilocus sequencing was isolated.
Invasive Aspergillosis Due to *N. udagawae*

(n = 12). The estimated duration of infection in this latter group ranged from 1.5 to 10 weeks (mean and median, 5.3 weeks; *P* < .05, Mann-Whitney *U* test). In all cases involving *N. udagawae*, there was radiological evidence of progressive disease across anatomical planes, with expansion or development of new infiltrates involving adjacent pulmonary lobes, pleurae, chest wall, and/or mediastinal structures (lymph nodes or vasculature). In patients 3 and 4, there was subsequent involvement of the contralateral lung and other organs. All patients underwent at least 3 modifications in antifungal regimens because of refractory disease.

Although conidial structures in the 4 strains of *N. udagawae* were similar to those of *A. fumigatus* (figure 3), the growth rate and colony morphology were different. All *N. udagawae* strains grew significantly slower than *A. fumigatus* sensu stricto at 37°C, and they produced cottony colonies with abundant fluffy aerial hyphae and poor conidiation, as opposed to velvety colonies of *A. fumigatus* with heavy conidiation. Such findings, however,

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**Figure 3.** Light microscopy with lactophenol cotton-blue staining of culture of *Neosartorya udagawae* (from patient 2, *A*; from patient 4, *C*) demonstrating morphologic features similar to those of *Aspergillus fumigatus* *sensu stricto* (*B*).

**Figure 4.** Mating study of clinical isolate (*A*, top and bottom quadrants) with mating-type reference strains of *Neosartorya udagawae* (*A*, left and right quadrants). Production of cleistothecia (*B*) confirmed multilocus sequence identification of *N. udagawae*.
Table 2. Antifungal susceptibility of Neosartorya udagawae clinical isolates.

<table>
<thead>
<tr>
<th>Source of isolate</th>
<th>AmB</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>Caspofungin</th>
<th>Micafungin</th>
<th>Terbinafine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.25</td>
<td>1</td>
<td>N</td>
<td>0.25</td>
</tr>
<tr>
<td>Patient 2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0.25</td>
<td>0.25</td>
<td>N</td>
<td>0.5</td>
</tr>
<tr>
<td>Patient 3</td>
<td>2</td>
<td>4</td>
<td>&gt;16</td>
<td>0.5</td>
<td>0.5</td>
<td>N</td>
<td>0.5</td>
</tr>
<tr>
<td>Patient 4</td>
<td>0.5–1</td>
<td>1</td>
<td>1–4</td>
<td>0.5</td>
<td>0.25–0.5</td>
<td>N</td>
<td>0.15–0.5</td>
</tr>
</tbody>
</table>

Aspergillus fumigatus sensu stricto

<table>
<thead>
<tr>
<th>Source of isolate</th>
<th>AmB</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>Caspofungin</th>
<th>Micafungin</th>
<th>Terbinafine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0.25</td>
<td>0.06–0.5</td>
<td>0.25–0.5</td>
<td>0.03–0.125</td>
<td>N</td>
<td>0.015</td>
<td>ND</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0.015</td>
<td>0.25</td>
<td>0.015</td>
<td>0.25</td>
<td>N</td>
<td>0.5</td>
<td>ND</td>
</tr>
<tr>
<td>Patient 3</td>
<td>0.015</td>
<td>0.25</td>
<td>0.015</td>
<td>0.25</td>
<td>N</td>
<td>0.5</td>
<td>ND</td>
</tr>
<tr>
<td>Patient 4</td>
<td>0.015</td>
<td>0.25</td>
<td>0.015</td>
<td>0.25</td>
<td>N</td>
<td>0.5</td>
<td>ND</td>
</tr>
</tbody>
</table>

NOTE. Data are minimum inhibitory concentrations or, for the echinocandins, minimal effective concentrations, expressed as mg/L. AmB, amphotericin B; ND, not determined.

* Composite result of 3 contemporary isolates from patients with chronic granulomatous disease who were undergoing selective antifungal testing.

cannot be considered specific for N. udagawae. Sequence analysis of the ITS1-5.8S-ITS2 rDNA region and benA and rodA genes from the isolates allowed their definitive identification. Although clinical isolates of N. udagawae may have poor mating capacity [14], 1 of our isolates mated successfully with type strain CBS-114218, producing abundant cleistothecia at the junction where the 2 strains met (figure 4), confirming that our isolate was indeed N. udagawae. Although the other 3 isolates failed to mate, multilocus sequencing results for these latter 3 were nearly identical to the former clinical isolate, confirming that all isolates were N. udagawae.

Antifungal susceptibility results demonstrated that N. udagawae was relatively resistant to AmB, itraconazole, and voriconazole, compared with A. fumigatus sensu stricto (table 2).

**DISCUSSION**

Survival rates for IA range from 40% to 70%; these low rates imply many cases of refractory disease, but the exact frequency is difficult to estimate. Host factors clearly impact clinical manifestations and outcome. However, pathogen phylogeny and accompanying differences in mold biology are emerging as important. Consequently, the heterogeneity of what is called IA, including refractory disease, may have poor mating capacity [13], and the molds from all 4 patients were initially identified as such. Poor in vitro sporulation, lack of microscopic structures that distinguish between A. fumigatus and N. udagawae, and poor mating capacity of clinical N. udagawae isolates impede timely and accurate identification. The mold from patient 4 was additionally identified as A. fumigatus via partial sequencing of the 28S rDNA by commercial kit. However, multilocus DNA sequence analysis clearly distinguished these 4 isolates of N. udagawae from A. fumigatus sensu stricto. A retrospective review of medical records unambiguously demonstrated that the clinical course for these cases was distinct from typical IA. This series illustrates the clinical relevance of Aspergillus taxonomy and the potential for this methodology to study the clinical impact of the infecting mold subspecies.

Invasive infections with fumigati-mimetics have been pre-
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient’s age, sex</th>
<th>Underlying disease</th>
<th>Infecting organism</th>
<th>Site of infection</th>
<th>Estimated duration of illness</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerber et al. 1973 [30]</td>
<td>57 years, M</td>
<td>NR</td>
<td>A. fischeri var. spinosus (N. pseudofischeri)</td>
<td>Lung</td>
<td>8 months (3 months while receiving therapy)</td>
<td>AmB</td>
<td>Survived</td>
</tr>
<tr>
<td>Coriglione et al. 1990 [31]</td>
<td>62 years, M</td>
<td>NR</td>
<td>N. fischeri var. fischeri (Wehmer) Malloch and Cain (N. pseudofischeri)²</td>
<td>Eye (keratitis progressing to endophthalmitis)</td>
<td>9 days</td>
<td>Oral and intravenousitraconazole</td>
<td>Enucleation</td>
</tr>
<tr>
<td>Summerbell et al. 1992 [32]</td>
<td>2 months, M</td>
<td>Tetralogy of Fallot requiring cardiac surgery</td>
<td>N. fischeri spinosa (N. pseudofischeri)²</td>
<td>Pulmonic valve endocarditis, pericardial graft, and myocardial necrosis</td>
<td>~7.5 weeks</td>
<td>AmB</td>
<td>Deceased</td>
</tr>
<tr>
<td>Padhye et al. 1994 [33]</td>
<td>77 years, M</td>
<td>History of silicosis and tuberculosis</td>
<td>N. pseudofischeri</td>
<td>Osteomyelitis of second and third lumbar vertebrae</td>
<td>~4.5 months</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lonial et al. 1997 [34]</td>
<td>48 years, M</td>
<td>Leukemia requiring allogeneic BMT, complicated by GVHD and multiple cases of bacteremia</td>
<td>N. fischeri</td>
<td>Skin (trunk, shoulders, arms), progressing to brain; on autopsy, multiple organs affected (heart, lungs, liver, spleen, thyroid, skin, brain)</td>
<td>32 days</td>
<td>AmB (625 mg total), changed to liposomal AmB because of progression of infection</td>
<td>Deceased</td>
</tr>
<tr>
<td>Chim et al. 1998 [35]</td>
<td>56 years, F</td>
<td>Multiple myeloma with chemotherapy-induced neutropenia</td>
<td>A. fischeri (N. fischeri)</td>
<td>Lung (BAL)</td>
<td>NR</td>
<td>AmB (and acyclovir for herpes simplex virus pneumonia)</td>
<td>Survived</td>
</tr>
<tr>
<td>Gori et al. 1998 [36]</td>
<td>42 years, M</td>
<td>Hepatitis C–associated cirrhosis requiring liver transplant, then retransplant, complicated by renal failure</td>
<td>N. fischeri</td>
<td>Lung (BAL), with dissemination to brain</td>
<td>2 weeks</td>
<td>Liposomal AmB and 5-fluorocytosine</td>
<td>Deceased</td>
</tr>
<tr>
<td>Guarro et al. 2002 [37]</td>
<td>75 years, F</td>
<td>NR</td>
<td>N. hiratsukae</td>
<td>Multifocal brain abscesses</td>
<td>~3 months</td>
<td>AmB, complicated by hyponatremia; changed to itraconazole; multiple surgical drainages</td>
<td>Initial clinical improvement; subsequently deceased from multiorgan failure, cause unidentified</td>
</tr>
<tr>
<td>Matsumoto et al. 2002 [38]</td>
<td>8 years, F</td>
<td>Peritoneal dialysis for renal failure from focal segmental glomerulosclerosis</td>
<td>N. pseudofischeri</td>
<td>Serosa of jejunum and peritoneal ascitic fluid</td>
<td>210 days</td>
<td>AmB, complicated by infusion reactions; changed to liposomal AmB; maintenance therapy with itraconazole</td>
<td>Protracted hospital course; repeated episodes of jejunal perforation; survived</td>
</tr>
<tr>
<td>Jarv et al. 2004 [39]</td>
<td>17 years, M</td>
<td>Hodgkin disease requiring second line chemotherapy for induction</td>
<td>N. pseudofischeri</td>
<td>Initially identified in blood; subsequent lung involve ment (CT halo sign and positive serum galactomannan)</td>
<td>32 days</td>
<td>AmB for 16 days, with improvement, followed by itraconazole</td>
<td>Infection resolved; relapse of Hodgkin disease</td>
</tr>
<tr>
<td>Balajee et al. 2005 [40]</td>
<td>NR</td>
<td>Leukemia requiring stem cell transplant</td>
<td>N. pseudofischeri</td>
<td>Ear biopsy (invasive otitis)</td>
<td>NR</td>
<td>AmB lipid complex, followed by voriconazole and caspofungin</td>
<td>Infection successfully treated; subsequently deceased from progressive leukemia</td>
</tr>
</tbody>
</table>

**NOTE.** BAL, bronchoalveolar lavage; BMT, bone marrow transplant; CT, computed tomograph; GVHD, graft-versus-host disease; NR, none reported.  
² Reidentified by Peterson as N. pseudofischeri on the basis of scanning electron microscopy of ascospores and on DNA complementarity [33].
vously reported in patients with various underlying diseases, involving *N. pseudofischeri* (anamorph, *Aspergillus thermomutatus*), *N. fischeri* (anamorph, *Aspergillus fischerianus*), and *N. hiratsukae* (anamorph, *Aspergillus hiratsukae*) (table 3). The estimated median duration of illness for these 3 organisms was 12.75, 3.3, and 12 weeks, respectively. The corresponding mortality rates were 2 (33%) of 6 patients with *N. pseudofischeri* and 2 (67%) of 3 patients with *N. fischeri*. *A. lentulus* was isolated from hematolymphoid transplant recipients, all of whom died despite receiving recommended therapy for IA [17]. Most *fumigati*-mimetic primary isolates produced fluffy white colonies because of abundant aerial hyphae with poor sporulation at room temperature and were presumptively identified as *Aspergillus* species or *A. fumigatus*. Accurate identification was predominantly by DNA analyses. Together with our series, these reports demonstrate the importance of molds that resemble *A. fumigatus* as distinct causes of IA and the difficulties in their identification.

Antifungal susceptibility data for the *fumigati*-mimetics are emerging. *N. pseudofischeri* displays higher MICs to voriconazole and possibly to AmB, compared with *A. fumigatus sensu stricto* [41]. *A. lentulus* demonstrates in vitro resistance to numerous antifungal agents [42]. *N. udagawae* from clinical specimens has higher MICs to AmB and voriconazole, although no clinical context was provided [14]. Thus, *fumigati*-mimetic molds tend to demonstrate in vitro resistance to antifungal agents routinely used in the treatment of IA, potentially contributing to refractory disease.

In this retrospective study, we parsimoniously estimated that the duration of illness dated from the recovery of previous isolates identified as *A. fumigatus* at the referring institutions and presumed these to be in fact *N. udagawae*, given the strong phenotypic resemblance between the 2 organisms. Because some of these isolates significantly predate patient evaluation at the National Institutes of Health, we were unable to successfully retrieve them to confirm identity. As a corollary, it is possible that the eventual isolation of *N. udagawae* from these patients was the result of selective pressure during successful treatment of previous episodes with *A. fumigatus sensu stricto*. However, the fact that *N. udagawae* was repeatedly isolated, over a prolonged period, from various specimens recovered from patients during hospitalization at our institution confirms that this mold can cause chronic infection.

*N. udagawae* and other *fumigati*-mimetics may account for a significant portion of refractory IA. Both deaths in our series were directly attributable to *N. udagawae*. 1 patient with CGD and 1 patient with myelodysplastic syndrome. Therefore, severe disease due to *N. udagawae* is not confined to a single immunodeficiency, unlike *A. nidulans* that is essentially restricted to CGD. The search for *fumigati*-mimetics in unusual or refractory IA is underway.

In summary, infection with *N. udagawae* can cause disease distinct from typical IA, being chronic and refractory with a propensity to spread across anatomic planes. Multilocus DNA sequence analysis permitted accurate identification. These observations have important implications for fungal identification in the clinical laboratory and in future studies of IA.

**Acknowledgments**

**Financial support.** Canadian Institutes of Health Research fellowship (to D.C.V.); National Institutes of Health Supplemental Visiting fellowship (to D.C.V.); Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health (N01-CO-12400); and National Cancer Institute, National Institutes of Health (HHSN261200800001E).

**Potential conflicts of interest.** All authors: no conflicts.

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