Fatal Endocarditis in a Neonate Caused by the Dematiaceous Fungus *Phialemonium obovatum*: Case Report and Review of the Literature

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*Phialemonium* species are grouped by most authorities among the dematiaceous fungi. Like several other darkly pigmented fungi, they appear to be an emerging cause of human disease, especially in the immunocompromised host. As numbers of immunocompromised patients increase, the trend of unusual fungi emerging as new pathogens is set to continue. Previous experience suggests that reports of rare fungal infections among selected patients often heralds the emergence of infection in a wider population of patients. We report a case of fatal endocarditis caused by *Phialemonium obovatum* in a premature neonate. To our knowledge this is the first documented case of native valve endocarditis due to this species, and we review the literature on invasive disease caused by the species. Unfamiliar fungal isolates are frequently misidentified or mistaken for environmental contaminants, and because of their relative rarity, data upon which to base antifungal treatment are limited. Thus, the diagnosis and treatment of unusual fungal pathogens present a significant challenge to clinicians and microbiologists alike. Early referral of such isolates to a specialist reference laboratory is advisable.

Among nosocomial mycotic infections there has been a gradual and significant shift away from *Candida albicans* towards non-*C. albicans* species and newer fungal opportunists (13, 14). Dematiaceous (dark-walled) fungi are an increasingly common cause of infection in immunocompromised hosts and transplant recipients (3, 16, 17, 19). Although *Phialemonium* species are pale in culture, melanin can be demonstrated in their cell wall by a special stain and they are considered true dematiaceous fungi. There are few reports documenting the role of *Phialemonium* species in invasive phaeohyphomycosis (infections caused by dematiaceous fungi). This may be due in part to microbiologists’ and clinicians’ lack of familiarity with unusual fungi, such as *Phialemonium* species, leading to their misidentification as nonpigmented filamentous molds or yeasts or their misdiagnosis as environmental contaminants. In addition to difficulties identifying clinical isolates, antifungal susceptibility data for *Phialemonium* species are limited, making optimal treatment recommendations problematic. As microbiological techniques for their detection and identification improve and awareness of their pathogenic potential increases, *Phialemonium* species are likely to emerge as increasingly important fungal pathogens. We report a case of fatal endocarditis in a premature neonate caused by *Phialemonium obovatum* and review the literature on invasive disease caused by *Phialemonium* species.

**Case report.** A 7-week-old boy, weighing 960 g, was transferred to the Neonatal Intensive Care Unit (NICU) of Children’s Memorial Hospital (CMH), Chicago, Ill., in March 2000 for further management of prematurity and failure to thrive. He was born prematurely at 28 weeks of gestation, weighing 1,050 g, to American parents, who were visiting family in rural Mexico. For the first month of life the infant was managed in a local hospital clinic with minimal neonatal facilities. He was never ventilated, was kept warm by swaddling without the aid of an incubator, and was fed by dropper. At 5 weeks of age and weighing 750 g, he developed necrotizing enterocolitis and was transferred to the NICU of the regional hospital. Enteral feedings were temporarily stopped and he was treated with intravenous dextroamphetamine and ceftazidime and given hyperalimentation via a right internal jugular central venous catheter (CVC).

On admission to CMH, the infant was symmetrically growth retarded, with weight, length, and head circumference below the 10th percentile for corrected gestational age. Physical examination revealed a temperature of 36.6°C, respiratory rate of 40/min in room air, heart rate of 134 beats/min, and normal heart sounds with no audible murmurs. Skin sutures were in situ in the right side of the neck at the site of the previous CVC.

Laboratory studies showed the following: hemoglobin, 10.6 g/dl; white blood cell count, 12,800/mm³ (neutrophils, 30%; bands, 3%); platelets, 290,000/mm³; reticulocyte count, 4.2%; and bicarbonate, 16 meq/liter with a normal anion gap. The metabolic acidosis was corrected with sodium bicarbonate.
FIG. 1. (A) Intraoperative photograph of fungal vegetation within right atrium. (B) Fontana-Masson stain of fungal vegetation demonstrating melanin pigmentation of cell wall of hyphae. Magnification, ×800.
Cranial ultrasound was normal save for a grade I intraventricular hemorrhage. Over the next 2 weeks the infant remained stable and demonstrated steady weight gain.

On the 18th hospital day, hepatomegaly, jaundice, and increased apneic episodes were noted. Laboratory studies revealed the following: hemoglobin, 6.4 g/dl; white blood cell count, 8,700/mm³ (neutrophils, 30%; bands, 3%); and platelets, 22,000/mm³. Red blood cell fragments and burr and target cells were seen on a peripheral blood smear, consistent with a microangiopathic hemolytic anemia. Bilirubin was 7.3 mg/dl (direct, 5.5 mg/dl); aspartate aminotransferase, 320 IU/liter; alanine aminotransferase, 178 IU/liter; gamma glutamyl transferase, 310 IU/liter; albumin, 2.4 g/dl; and prothrombin time, 16.7 s. Blood and urine bacterial and fungal cultures were sterile. The infant received red blood cell and platelet transfusions.

Four days later, on day 22, tachypnea and increasing respiratory distress developed, and auscultation of the heart revealed a gallop rhythm and a II/VI systolic murmur with a midsystolic click. Echocardiography demonstrated a 1.1- by 0.8-cm pedunculated right atrial mass that was adherent to the tricuspid valve and moved in and out of the right ventricle with the cardiac cycle. Doppler ultrasound demonstrated an additional thrombus partially obstructing the superior vena cava. Anticoagulation with low-molecular-weight heparin was started. Although the infant remained hemodynamically stable and afebrile, persistent thrombocytopenia and anemia required daily platelet and frequent red blood cell transfusions.

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On the 28th hospital day, gram-variable yeast-like cells were identified in blood cultures, and treatment with intravenous amphotericin B (1 mg/kg of body weight/day) was started. Subsequent subculture on 5% sheep blood and Sabouraud dextrose agars incubated at 24 to 25°C demonstrated the characteristic appearance of a mold. Initially, on the basis of the yellowish-white colony and the production of long tapering phialides, the isolate was identified tentatively as an Acremonium species. Over the next 2 weeks, fungemia persisted (days 30 to 32 and 35 to 42) despite treatment with escalating doses of liposomal amphotericin B from 5 to 15 mg/kg/day. Repeat echocardiography demonstrated increased size of the tricuspid vegetation (to 1.8 by 1.2 cm), obstruction of the tricuspid valve, and right-to-left shunting across a patent foramen ovale. Hypotension and respiratory failure necessitated intubation and ventilation, and the infant underwent emergency open-heart surgery to resect the right atrial mass.

Postoperative blood cultures continued to grow fungus (days 43, 45, 46, 48, and 49) and signs of disseminated fungal disease became apparent: Urine culture grew fungus (day 44) and renal and cranial ultrasounds demonstrated multiple echogenic foci in the kidneys and in the distribution of both middle cerebral arteries. Cardiorespiratory failure and metabolic acidosis worsened, and the infant died 9 days after cardiac surgery (7 weeks after admission to CMH). An autopsy was not performed.

**Results.** The initial sample, a blood culture, demonstrated gram-variable yeast-like cells after 72 h of incubation in broth at 37°C (Bactec; Becton Dickinson, Baltimore, Md.). Subsequent subculture on 5% sheep blood and Sabouraud dextrose agars demonstrated the characteristic appearance of a mold. Initially, on the basis of the yellowish-white colony and the production of long tapering phialides, the isolate was identified tentatively as an Acremonium species. Over the next 2 weeks, fungemia persisted (days 30 to 32 and 35 to 42) despite treatment with escalating doses of liposomal amphotericin B from 5 to 15 mg/kg/day. Repeat echocardiography demonstrated increased size of the tricuspid vegetation (to 1.8 by 1.2 cm), obstruction of the tricuspid valve, and right-to-left shunting across a patent foramen ovale. Hypotension and respiratory failure necessitated intubation and ventilation, and the infant underwent emergency open-heart surgery to resect the right atrial mass.

At surgery, a soft, friable yellow-green mass (measuring 2.0 by 1.5 by 1.0 cm) was removed from the septal and posterior leaflets of the tricuspid valve (Fig. 1A). Histology showed a fibrinous acellular mass that on Gomori methenamine-silver periodic acid-Schiff staining was composed of masses of branching, slender septate fungal hyphae. The presence of melanin in the cell walls of the hyphae was demonstrated by Fontana-Masson stain (Fig. 1B).

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**FIG. 2.** Photomicrograph of *P. obovatum* isolate showing obovate straight conidia (3.5 to 5 by 1 to 2 μm) (arrow) borne on adelophialides (reduced phialides lacking a basal septum) (arrowhead). Magnification, ×920.
Subsequently, the fungal isolate was formally identified by the Fungus Testing Laboratory at the University of Texas Health Sciences Center in San Antonio (UTHSC) as *P. obovatum* (UTHSC accession number 00-1658) based upon its macroscopic and microscopic morphology. Specifically, cream-colored to pale yellow, somewhat moist colonies produced a distinct green diffusible pigment in culture (10 days at 25°C in potato flakes agar), consistent with the previously described features for the species (Fig. 2 and 3). Diagnostic microscopic characteristics included obovate (like an upside-down egg), consistently straight conidia (3.5 to 5 by 1 to 2 μm) that were borne primarily from adelophialides (reduced phialides lacking a basal septum) rather than discrete phialides (Fig. 2).

Fungal susceptibility testing was performed at the Fungus Testing Laboratory at the UTHSC by a broth macrodilution method (NCCLS standard M38-P; 25°C). The 48-h MICs were 2 μg/ml for ketoconazole, 32 μg/ml for fluconazole, >16 μg/ml for amphotericin, >64 μg/ml for flucytosine, and 1 μg/ml for itraconazole.

**Discussion.** The genus *Phialemonium* was first described in 1983 by Gams and McGinnis as having morphological features intermediate between fungi of the genera *Acremonium*, which are hyaline or nonpigmented, and *Phialophora*, which are pigmented species (4). *Phialemonium* species are considered by most authorities to be dematiaceous fungi (with melanin in the cell walls and septa of their hyphae) (2). However, the innate hyphal pigmentation is demonstrable in tissue only by histological stains that have specificity for melanin, such as the Fontana-Masson silver stain, which may not be entirely satisfactory in all cases (10, 20). It is suggested that the antioxidant properties of melanin are a virulence factor for the dematiaceous fungi (17).

At present, two *Phialemonium* species, *P. obovatum* and *P. curvatum*, are distinguished on the basis of colony color, conidial morphology, and molecular markers (5). Unlike most of the medically important dematiaceous fungi, which are olive green or brown to grey-black, *P. obovatum* produces a distinctive pale green pigment in culture. The characteristic conidium-producing cells in *Phialemonium* species are known as adelophialides, which arise from hyphal cells as a short lateral neck or peg without a basal septum. As the name implies, the conidia of *P. obovatum* are obovoid, or narrowest at the base (2, 4). In culture, *Phialemonium* species have the added ability to sporulate within the matrix of the agar medium, without the requirement of an air space above the hyphae (4). This property is also found in the hyaline filamentous molds, such as *Fusarium*, and the more closely related *Acremonium* species (6, 17). It is suggested that *Fusarium* and *Acremonium* species are more frequently associated with fungemia than angioinvasive fungi, such as *Aspergillus* and *Mucor*, because of their ability to produce unicellular yeast-like forms or propagules in vivo that can circulate in the bloodstream more readily than hyphal structures (8, 13, 17). Although this property has not yet been demonstrated for *Phialemonium* species, budding yeast-like forms of *P. obovatum* have been observed in vivo (7) and were demonstrated in blood cultures from the present case.

*Phialemonium* species are saprobes in nature and have been isolated from soil, sewage, air, and water (4). Among dematiaceous fungi, the maximum growth temperature is often used to distinguish potential pathogens from probable contaminants. Dematiaceous species that can grow at 35°C and higher may become invasive and disseminate; those that cannot are usually nonpathogenic or restricted to causing superficial mycoses. *Phialemonium* species have the ability to grow in culture at temperatures as high as 40°C, indicating not only their pathogenicity but perhaps their potential for infection of the central nervous system as well (2).

There are relatively few documented reports of invasive
disease caused by *Phialemonium* species (Table 1). The first was in a 4.5-month old infant with fatal *P. obovatum* infection of thermal burn wounds, viable tissue, and blood vessels, with dissemination to the spleen (11). Recent reports have demonstrated the ability of *Phialemonium* species to cause disease in other immunocompromised hosts and even in the occasional previously healthy patient. For example, *Phialemonium* species have been reported as a cause of invasive disease in two renal transplant patients: a 5-year-old girl with fungal peritonitis related to a dialysis catheter and a 50-year-old woman with osteomyelitis of the foot (7). *P. obovatum* osteomyelitis has been observed in a previously healthy 41-year-old man following diskography (10). Fatal *P. curvatum* and *Streptococcus sanguis* endocarditis of a porcine bioprosthetic aortic valve in a 63-year-old woman has been described (18). Finally, CVC-related nosocomial *P. curvatum* fungemia has been observed in a 41-year-old patient with relapsed acute lymphocytic leukemia and in a 37-year-old stem cell transplant recipient from the same hospital (5).

The increase in reports of invasive disease caused by *Phialemonium* species, the parallel increase in frequency of phaeohyphomycoses in general, and the continued increase in the numbers of susceptible immunocompromised patients suggest that *Phialemonium* species are an emerging cause of human disease. Cases of invasive mycoses caused by *Phialemonium* species exhibit many features frequently associated with other fungal opportunists. Specifically, four of the seven previously documented cases of *Phialemonium* infection occurred in immunocompromised patients: two renal transplant recipients and two patients with hematologic malignancies, one of whom had had a previous stem cell transplant. In the remaining cases, the natural mechanical barrier of the skin was compromised by burns or invasive procedures. Finally, the propensity of *Phialemonium* species to produce disease in abnormal or unexpected sites and the nosocomial nature of these infections are notable. The association with catheters and prosthetic valve infections suggests that *Phialemonium* species are similar to the closely related *Acremonium* species, which are a common cause of catheter infections (1, 6, 9, 12, 15, 17), in the ability to attach to plastic or foreign materials.

Neonates are immunocompromised and at high risk for invasive fungal disease, especially if they are premature or have low birth weight. In the NICU setting, neonates undergo an increasing array of invasive diagnostic and therapeutic procedures and are exposed to both broad-spectrum antimicrobial agents and resistant microorganisms. Moreover, advances in neonatology have led to greater numbers of premature infants surviving, and these infants are then susceptible to infection with emerging opportunistic pathogens. *Phialemonium* species should be added to the list of potential causes of fungal infections in this population.

Recognition and identification of *Phialemonium* species present a significant challenge for the clinician and microbiologist alike. Similarly, the presence of different morphological forms of fungi in unusual anatomic sites and the apparent absence of melanin pigmentation make its identification in tissue problematic. Thus, it is conceivable that without special histological stains or the help of a fungal reference laboratory, many clinical isolates of *Phialemonium* species may either be misidentified as hyaline filamentous fungi, such as *Acremonium* species, or be misdiagnosed as laboratory contaminants. In the absence of definitive identification of an unusual fungus, the choice of optimal antifungal therapy remains difficult. Furthermore, because *Phialemonium* species are rare clinical isolates, there are no definitive data upon which to base recommendations for optimal treatment. The limited results of fungal susceptibility testing, where they exist, suggest that *P. obovatum* is resistant to both amphotericin B and itraconazole.

### TABLE 1. Cases of invasive disease caused by *Phialemonium* species

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age and sex</th>
<th>Species</th>
<th>Predisposing condition</th>
<th>Type of infection</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>4.5 mo, M</td>
<td><em>P. obovatum</em></td>
<td>Burns</td>
<td>Sepsis</td>
<td>Surgery</td>
<td>Death</td>
</tr>
<tr>
<td>7</td>
<td>50 yr, F</td>
<td><em>P. curvatum</em></td>
<td>RT</td>
<td>Bone cyst</td>
<td>Surgery</td>
<td>Care</td>
</tr>
<tr>
<td>7</td>
<td>5.5 yr, F</td>
<td><em>P. obovatum</em></td>
<td>RT, dialysis catheter</td>
<td>Peritonitis</td>
<td>AMB, KTC, FLC</td>
<td>Cure</td>
</tr>
<tr>
<td>10</td>
<td>41 yr, M</td>
<td><em>P. obovatum</em></td>
<td>Diskography</td>
<td>Osteomyelitis</td>
<td>Surgery</td>
<td>Cure</td>
</tr>
<tr>
<td>18</td>
<td>63 yr, F</td>
<td><em>P. curvatum</em></td>
<td>Prosthetic heart valve</td>
<td>Endocarditis</td>
<td>None</td>
<td>Death</td>
</tr>
<tr>
<td>5</td>
<td>41 yr, M</td>
<td><em>P. curvatum</em></td>
<td>ALL, CVC</td>
<td>Fungemia</td>
<td>AMB</td>
<td>Death</td>
</tr>
<tr>
<td>10</td>
<td>37 yr, M</td>
<td><em>P. curvatum</em></td>
<td>Hodgkins, SCT, CVC</td>
<td>Fungemia</td>
<td>ITC</td>
<td>Cure</td>
</tr>
<tr>
<td>This study</td>
<td>7 wk, M</td>
<td><em>P. obovatum</em></td>
<td>Prematurity, NEC, CVC</td>
<td>Endocarditis</td>
<td>Surgery, AMB</td>
<td>Death</td>
</tr>
</tbody>
</table>

* ALL, acute lymphatic leukemia; CVC, central venous catheter; NEC, necrotizing enterocolitis; RT, renal transplant; SCT, stem cell transplant; AMB, amphotericin B; FLC, fluconazole; ITC, itraconazole; KTC, ketoconazole.

### TABLE 2. Antifungal susceptibilities of invasive clinical isolates of *Phialemonium* species

<table>
<thead>
<tr>
<th>Species</th>
<th>MIC (μg/ml)*</th>
<th>Reference</th>
<th>Accession no.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMB</td>
<td>ITC</td>
<td>FLC</td>
</tr>
<tr>
<td><em>P. curvatum</em></td>
<td>0.25</td>
<td>&gt;40</td>
<td>&gt;40</td>
</tr>
<tr>
<td><em>P. obovatum</em></td>
<td>&gt;18.47</td>
<td>1.25</td>
<td>40</td>
</tr>
<tr>
<td><em>P. obovatum</em></td>
<td>36.94</td>
<td>1.25</td>
<td>&gt;80</td>
</tr>
<tr>
<td><em>P. curvatum</em></td>
<td>0.25</td>
<td>0.06</td>
<td>16</td>
</tr>
<tr>
<td><em>P. curvatum</em></td>
<td>0.5</td>
<td>0.06</td>
<td>16</td>
</tr>
<tr>
<td><em>P. obovatum</em></td>
<td>&gt;16</td>
<td>1</td>
<td>32</td>
</tr>
</tbody>
</table>

* AMB, amphotericin B; FLC, fluconazole; 5-FC, fluycytosine; ITC, itraconazole; KTC, ketoconazole; NT, not tested.
while the susceptibility results for *P. curvatum* for itraconazole and ketoconazole appear somewhat contradictory (Table 2). Finally, results of in vitro fungal susceptibility tests do not always correlate with in vivo antifungal activity.

In the present case, in addition to early surgical intervention, high-dose fluconazole might have been a better treatment option, had definitive identification and antifungal susceptibility data been available. However, initial identification of the isolate as an *Acremonium* species, which are uniformly resistant to fluconazole (6), led to continuation of therapy with amphotericin B, to which the isolate was later found to be resistant. In addition, because ketoconazole can be administered only enterally, it would not have been a feasible therapeutic option, despite in vitro sensitivity.

Previous experience suggests that reports of rare fungal infections among selected patient subgroups and animals are proven predictors of potential emerging pathogens and the harbinger of future infection in a wider patient population (17). The recent increase in reports of infections with *Phialemonium* species and continued expansion of the number of immunocompromised patients suggests that infection with these unfamiliar fungal pathogens is likely to become more widespread. The lack of uniform susceptibility of *Phialemonium* species to amphotericin B and itraconazole, the usual antifungal agents (and perhaps synergy studies) is required to identify the best therapeutic regimen. The present case emphasizes the inherent difficulty of managing infections caused by unusual or unfamiliar fungal pathogens and the importance of timely referral to reference laboratories for formal identification and standardized susceptibility testing.

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REFERENCES


