Fatal Hormonema dematioides Peritonitis in a Patient on Continuous Ambulatory Peritoneal Dialysis: Criteria for Organism Identification and Review of Other Known Fungal Etiologic Agents

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We report a fatal case of fungal peritonitis caused by the yeast-like dematiaceous mold Hormonema dematioides in a 45-year-old woman. The woman had a 13-year history of insulin-dependent diabetes mellitus and had been on continuous ambulatory peritoneal dialysis for chronic renal failure. H. dematioides was repeatedly isolated from the dialysate culture specimens collected on days 3, 9, 16, and 20 of her hospital stay. Preliminary culture reports on day 7 of the growth of a yeast-like fungus, a probable Candida species, prompted the administration of fluconazole (FLU). Intraperitoneal and intravenous FLU failed to eliminate the mould, and the patient expired on day 21 of her hospital stay. We use this case to present what appears to be the first report of fungal peritonitis due to H. dematioides, to provide laboratorians with criteria for differentiating this organism from the similar mold Aureobasidium pullulans and from various yeast genera, and to provide a review of known fungal taxa inciting peritonitis.

Fungal peritonitis is a serious and potentially life-threatening complication of both intermittent peritoneal dialysis and continuous ambulatory peritoneal dialysis (CAPD). Investigators reviewing significant numbers of CAPD-associated fungal peritonitis episodes cite yeasts, particularly Candida species, as the predominant etiologic agents (10, 12, 13, 20, 29, 37, 38, 50, 52, 53, 54, 58, 61, 63, 65, 66, 68, 73, 78). filamentous fungi complicating CAPD, although reported less frequently and fewer in number, encompass a wide array of agents, from the classic, systemic pathogens (4, 42, 45) to zygomycetous species (55, 64) and members of numerous moniliaceous (3, 11, 16, 25, 27, 30, 33, 39, 40, 48, 51, 57, 67, 71, 75, 76, 77) and dematiaceous genera (1, 2, 6, 7, 14, 21, 28, 31, 33, 39, 43, 44, 59, 69, 80). See Table 1 for a listing of reported etiologic agents of fungal peritonitis. filamentous Candida-associated fungi displaying cream-colored (moniliaceous) colonies and yeast-like synanamorphs may initially be considered Candida or Cryptococcus species. Two such organisms, Hormonema dematioides Lagerberg et Melin [teleomorph, Sydowia polyspora (von Tavel) Müller], the subject of this report, and Aureobasidium pullulans (deBary) Arnaud, are treated intraperitoneally for 20 days without clinical improvement. Upon admission from the emergency room, the patient’s dialysate cell count was 306/μl, with a predominance of polymorphonuclear neutrophils (70%). The hemoglobin level was 6.6 g/dl, the leukocyte count was 6,700/μl, the blood urea nitrogen level was 12.1 mg/dl, and the serum creatinine level was 5.0 mg/dl. The patient was initially treated with intraperitoneal ceftazidime and imipenem. Fluconazole therapy was started on hospital day 7, following a preliminary culture report indicating the presence of a yeast-like fungus, probably a Candida species, in the dialysate. Dialysate cell counts on day 6 were 2,600/μl, with a predominance of polymorphonuclear neutrophils. On day 8, the patient’s abdominal pain and fever slightly improved, but vasopressive drug and O2 therapies were started due to the occurrence of respiratory insufficiency and hypotension. Dialysate cell counts were 675 and 441/μl on days 9 and 17, respectively. The same yeast-like fungus was cultured from the dialysate on days 3, 9, 16, and 20. Fluconazole was administered intraperitoneally (200 mg/day) for 15 days and intrave-
nously (800 mg/day) for the last 2 days. The catheter tip was removed on day 20. On day 21 the patient began to lose consciousness, appeared to have signs of acute respiratory insufficiency due to hypoxia and septic shock, and expired. Blood cultures for the causative organism remained negative.

**Mycology.** All four peritoneal fluid culture specimens collected during the patient's hospital stay (on days 3, 9, 16, and 20) revealed the same organism. Three of the dialysates were inoculated onto Sabouraud dextrose agar (SDA) (Becton Dickinson, Towson, Md.). Only the BACTEC 16A bottle (aerobic medium) was positive after 48 h of incubation. Pure growth of cream-colored mucoid colonies was observed on SDA and on the blood agar plate subculture from the BACTEC 16A in 24 to 48 h at 35°C. Growth at 35°C was slow, and a Gram stain of organisms from the colony revealed oval-shaped yeast forms. API 20C yeast identification system strips, tested a total of seven times with identical results, indicated assimilation of glucose, glyceral, 2-keto-gluconate, D-arabinose, D-xylose, adonitol, xylitol, galactose, inositol, sorbitol, cellobiose, maltose, saccharose, trehalose, melibiose, and raffinose, giving a numerical code of 6773277. The API database, which provides a list of species and their probabilities, with a confidence estimate for each identification, indicated the code as an unacceptable profile with no identification. Ancillary testing on cornmeal agar (Difco Laboratories, Detroit, Mich.) by the Dalmau method (17) indicated the presence of hyphae and blastic conidia. Conidia occurred asynchronously from the hyphae as viewed under the coverslip after 72 h of incubation at 25°C (Fig. 2). Prolonged incubation of the isolates for 1, 2,
and 3 weeks on SDA revealed their dematiaceous nature (Fig. 3). Subsequent subcultures of the isolate at 25°C were totally brown to black. A 5-day slide culture revealed the presence of moniliaceous blastic conidia being produced from dematiaceous hyphae (Fig. 4).

**Pathogenicity and identifying features.** Fungal peritonitis in patients on CAPD, although significantly less frequent than bacterial peritonitis (3 to 15% versus >80%, respectively), is a well-documented clinical entity (13, 38, 54, 65, 78). Signs and symptoms are essentially the same in both presentations and may include cloudy dialysate effluent, dialysate leukocyte counts greater than 100/mm³, neutrophil counts greater than 50%, abdominal pain, distension, rigidity, nausea and vomiting, diarrhea, and fever. Because of these similarities and the higher incidence of bacterial peritonitis, fungal etiologies may be overlooked and may have contributed, in part, to a delayed antifungal regimen in the case of this patient. She received cefazolin and vancomycin intraperitoneally for 20 days, without improvement, followed by ceftazidime and imipenem intraperitoneally for another 7 days. Not until hospital day 7 (episode day 28), with the report of a *Candida* species in the dialysate, was fluconazole therapy started. Although the route of infection is not clear, several reports have cited altered host flora due to prior or prolonged use of broad-spectrum antibacterial therapy as a significant risk factor and/or as being associated with the development of fungal peritonitis (13, 38, 54, 65, 78). Fungal cultures taken earlier in the course of this patient’s episode or during the administration of antibacterial agents would have provided direction for more appropriate or additional antifungal therapy.

The recovery of cream-colored, mucoid colonies from the dialysate on hospital day 7 (episode day 28) provided the first evidence of a fungal pathogen. Cream-colored mucoid colonies are consistent with a variety of fungal genera, both yeast-like and filamentous, including *Candida*, *Cryptococcus*, *Aureobasidium*, and *Hormonema*. In the genera *Aureobasidium* and *Hormonema*, cream-colored colonies become brownish to olivaceous black with time, thereby requiring extended incubation for recognition of their dematiaceous nature. The API 20C yeast identification system utilized with these colonies failed to provide an identification, giving an unrecognizable code of 6773277. McCarthy et al. recently reported on 4 of 11 isolates of *H. dematioides* coding as *C. albicans* by this method (49). The remaining 7 isolates in their group revealed several different unrecognizable codes, which did not include this isolate’s number, 6773277. Their results reinforce the necessity of performing critical microscopic observations (for blastic conidia, hyphae, pseudohyphae, etc.) and demonstrate the futility of relying solely on binary codes and/or physiologic characteristics for these similar, cream-colored, mucoid taxa. Because the API 20C method failed to provide an identification, the case isolate was subsequently identified by ancillary testing utilizing the Dalmau method for determining the method of conidiogenesis and extended incubation for revealing its dematiaceous affinities. Slide culture preparations normally used for studying methods of conidiogenesis in filamentous fungi
<table>
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<th>Species</th>
<th>Macroscopic morphology</th>
<th>Microscopic morphology</th>
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<tr>
<td>Hormonema dematioides</td>
<td>Creamy, moist, mucoid, white to cream initially, becoming brown to black</td>
<td>Hyphae hyaline and dematiaceous; hyaline, oval-shaped blastic conidia, asynchronous, from hyaline and dematiaceous hyphae; nonbudding</td>
<td>Cycloheximide 25°C 35°C 42°C Urease Nitrate Glucose fermentation methyl-α-Glucoside d-Gluconate</td>
<td>Cornmeal agar Dalmau plate to determine method of conidiogenesis</td>
<td>18, 19, 32, 62</td>
</tr>
<tr>
<td>Aureobasidium pullulans</td>
<td>Creamy, moist, white to cream initially, becoming partly brown to black (frequently with a white, radiating fringe at the periphery)</td>
<td>Hyphae hyaline and dematiaceous; hyaline, oval-shaped blastic conidia, synchronous, from hyaline hyphae only; nonbudding</td>
<td></td>
<td></td>
<td>18, 19, 32, 62</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>Cream colored, numerous phenotypes (dry, wrinkled, mucoid)</td>
<td>Variably sized, globose to oval budding yeast; pseudohyphae and true hyphae; germ tube positive</td>
<td></td>
<td>Numerous other yeast species are etiologic agents of CAPD-associated fungal peritonitis</td>
<td>62, 74</td>
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<tr>
<td>Cryptococcus albidus</td>
<td>Cream-colored to beige to slight pink, mucoid colonies</td>
<td>Large, round budding yeast; no true hyphae or pseudohyphae</td>
<td></td>
<td>Some H. dematioides isolates may code as C. albidus by API 20C</td>
<td>49, 62, 74</td>
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<tr>
<td>Candida parapsilosis</td>
<td>Cream-colored, moist</td>
<td>Branched pseudo-hyphae, oval budding yeast</td>
<td></td>
<td>A common yeast negative for growth on cycloheximide yeast that could be confused with H. dematioides</td>
<td>74</td>
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* On SDA.
* Cornmeal agar, Dalmau method.
* Physiology was studied under the following conditions: on medium with cycloheximide; at 25, 35, and 42°C; on Christensen’s urea agar slant (Urease); and by the method of Pincus et al. (62) (Nitrate). Results are reported as follows: −, negative; +, positive; V, variable; W, weak; NG, no growth; and G, growth.
are generally less satisfactory than the Dalmau method for visualizing the asynchronous or synchronous development of conidia in *Hormonema* and *Aureobasidium* species, respectively.

*H. dematioides* is an important wood-bleuing fungus often isolated from discolored coniferous wood or needles (32). It is also appears to occupy an ecological niche in moist environments, as evidenced by the isolates submitted to the Fungus Testing Laboratory (FTL) at the University of Texas Health Science Center at San Antonio from high-humidity areas. Its pathogenicity in humans has been previously documented as an agent of subcutaneous phaeohyphomycosis of the hands of an immunocompetent host (15). Additional human sites from which the organism has been recovered include cerebrospinal fluid, blood, stool, pleural fluid, a surgical wound, and a knee (FTL isolates [unpublished data]).

Because authors have illustrated *H. dematioides* under the name of *A. pullulans*, some cases of infection ascribed to *A. pullulans* may actually have been caused by misidentified isolates of *H. dematioides*. Recently Clark et al. described a case of peritonitis caused by *A. pullulans* in a patient on CAPD (14). Caporale et al. reported *A. pullulans* as an agent of peritoneal catheter colonization and peritonitis (7). The present case demonstrates that *H. dematioides* can also cause CAPD-associated peritonitis. The pure growth of the organism from four separate specimens from a patient who had diffuse abdominal pain and turbid dialysates indicates that it was the cause of peritonitis and not a contaminant.

Colonies on SDA at 25°C are white to cream, smooth, and soon covered with a light slimy mass of blastoconidia. Poorly conidiating cultures are olivaceous black with a wooly mycelial mat. The optimum temperature for growth is 24°C, with a daily growth rate of >6 mm; no growth is observed on media containing cycloheximide. Isolates that have been subcultured repeatedly conidiate poorly and tend to grow faster than freshly isolated strains (32). Microscopically, hyphae are septate, hyaline, and initially thin walled and soon become brown and thick walled, with cells wider than they are long. Hyaline, smooth, ellipsoidal blastic conidia (4.5 to 12 µm by 3 to 4.5 µm) are borne asynchronously by percurrent proliferation (each successive conidium growing through the tip of the conidia genus) from mostly intercalary conidiogenous loci on hyaline as well as dematiaceous hyphae (Fig. 4). Older conidia often swell and become brown and are frequently two celled. Endoconidia (conidia formed inside hyphal cells) may be present. The method of conidiogenesis for both *A. pullulans* and *H. dematioides* is best studied by the Dalmau method. *H. dematioides* is differentiated from *A. pullulans* by asynchron-ous, basipetal (youngest conidium at the base) conidal formation from both hyaline and dematiaceous hyphae rather than synchronous (all at the same time) conidial formation from only hyaline hyphae. Synchronous conidia appear as a cluster, with each member attached to a separate denticle, while asynchronous conidia appear as a detached cluster around an individual conidiogenous aperture. Also note that several other *Hormonema* species exist, but all grow <6 mm per day at 24°C. Both *H. dematioides* and *A. pullulans* are differentiated from hyaline, mucoid yeasts by the formation of dematiaceous hyphae (Table 2).

**Therapy.** Fungal peritonitis is associated with significant morbidity and mortality. In the patient this report, intraperitoneal fluconazole (200 mg/day for 15 days) followed by intravenous fluconazole (800 mg/day for 2 days) therapy failed to improve the clinical conditions. Retrospectively, higher empiric doses earlier may have been more efficacious, as judged by data from yeast isolates that exhibit dose-dependent susceptibility to fluconazole and that therefore require maximum dosing regimens (70). Catheter removal, considered a necessary adjunct to antifungal therapy (11, 37, 38, 54, 77), was delayed because there was no other therapeutic option for renal failure in this patient. The patient had severe, frequent hypotension histories associated with the arteriovenous shunt, severe malnutrition, and extensive peritoneal adhesions. Treatment of fungal peritonitis caused by rare fungi such as *H. dematioides* is complicated by problems in identification, the lack of in vitro antifungal susceptibility data, empiric therapy which may not be appropriate (24), and the reluctance to initiate amphotericin B therapy until a final identification is made. Although standardization of susceptibility testing for filamentous fungi is only beginning (23) and in vivo therapy correlations are lacking, a significant number of dematiaceous moulds appear to be susceptible, in vitro, to itraconazole (74).

Although the case isolate was not available for testing against antifungal agents, data from the FTL for five similar dematiaceous *A. pullulans* isolates tested by a modified National Committee for Clinical Laboratory Standards reference method (56) suggest greater in vitro susceptibility to itraconazole. Had the filamentous and dematiaceous nature of the etiologic agent been known earlier, the institution of itraconazole therapy, with or without amphotericin B, may have facilitated deference. Several reports cite its use in CAPD-associated fungal peritonitis (12, 22, 28, 39, 67, 77).

Although filamentous fungal organisms in CAPD-associated peritonitis are low in incidence, they are often associated with significant morbidity and/or mortality. As this case emphasizes, consideration of a fungal etiology early in the course of the disease, particularly in patients unresponsive to antibacterial therapy, is crucial. Early recognition and identification of the etiologic agent, coupled with appropriate, aggressive therapy (antifungal therapy and catheter removal, when possible), appear tantamount to a successful outcome. *H. dematioides* is yet another dematiaceous agent that incites CAPD-associated fungal peritonitis.

**REFERENCES**


