Peritonitis Due to *Curvularia inaequalis* in an Elderly Patient Undergoing Peritoneal Dialysis and a Review of Six Cases of Peritonitis Associated with Other *Curvularia* spp.

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Fungal peritonitis due to *Curvularia* species in patients undergoing peritoneal dialysis is a very rare problem. We report a case of peritonitis caused by *Curvularia inaequalis*. This is the first report in the English literature of this species causing human infection. We also review the six previously reported cases of continuous ambulatory peritoneal dialysis peritonitis caused by other *Curvularia* species.

CASE REPORT

An 85-year-old woman was on continuous ambulatory peritoneal dialysis for end-stage renal failure due to renovascular disease. Her past medical history included hypertension, hypothyroidism, cholelithiasis, left ventricular failure, and a left-sided stroke with minimal residual deficit. She had commenced continuous ambulatory peritoneal dialysis 2 years prior and performed peritoneal exchanges independently. During that period, there had been multiple episodes of suspected peritonitis, each treated empirically with a single dose of intraperitoneal (i.p.) antibiotics. However, one episode, in December 2003, was confirmed by culture as being caused by *Staphylococcus epidermidis*. These episodes were believed to have been the result of poor aseptic techniques that led to contamination.

The patient presented on March 14, 2004, at the emergency department at Geelong Hospital in Victoria, Australia, with a 3-day history of abdominal pain, accompanied by fever and nausea, and cloudy peritoneal dialysis (PD) bags. On examination, she was found to be febrile (37.8°C) with a tense abdomen, rebound tenderness, and decreased bowel sounds. The Tenckhoff catheter site was clean with no sign of inflammation. Full blood examination showed an elevated white cell count (WCC): 15.1×10^6/liter with 84% neutrophils. The C-reactive protein level was raised to 90 mg/liter, and the albumin level was 24 g/liter. The urea level was 15.3×10^6 mmol/liter, and the creatinine level was 462×10^6 μmol/liter. The fluid in the PD bag was pale yellow, cloudy with fibrous material, and slow to drain. The PD fluid was sent for microscopy and culture and found to have a WCC of $2,328 \times 10^6$/liter with 108×10^6 red blood cells/liter. No organisms were observed with the use of the Gram stain.

The patient was admitted into the hospital with presumed bacterial peritonitis and started on a peritonitis protocol consisting of i.p. cephazolin, gentamicin, and heparin. On day 6 after admission, a single dose of i.p. vancomycin was given empirically for persisting peritonitis, turbid effluent with a rising WCC, and fever. Meanwhile, the patient continued to deteriorate, became progressively malnourished, and developed the complications of small-bowel ileus and paroxysmal atrial fibrillation. In light of the worsening prognosis, the patient and family decided to request that a not-for-resuscitation order be put in place.

During this patient's stay, six samples of PD fluid were sent for microscopy and culture. No significant organisms were detected in the initial sample. Growth was detected in the second
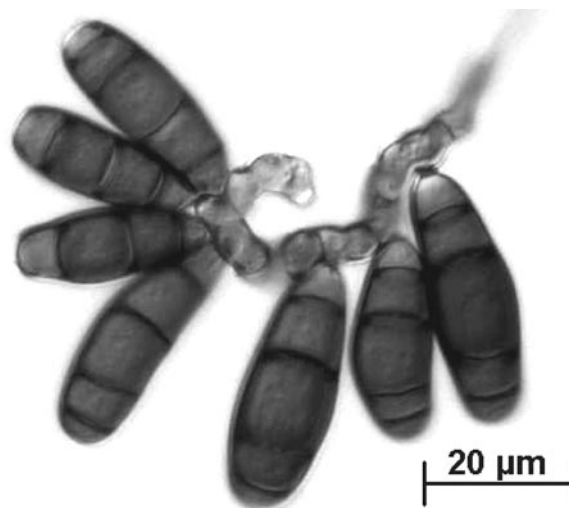

FIG. 1. *C. inaequalis* UAMH 10438 showing septate conidia borne on a geniculate conidiophore.

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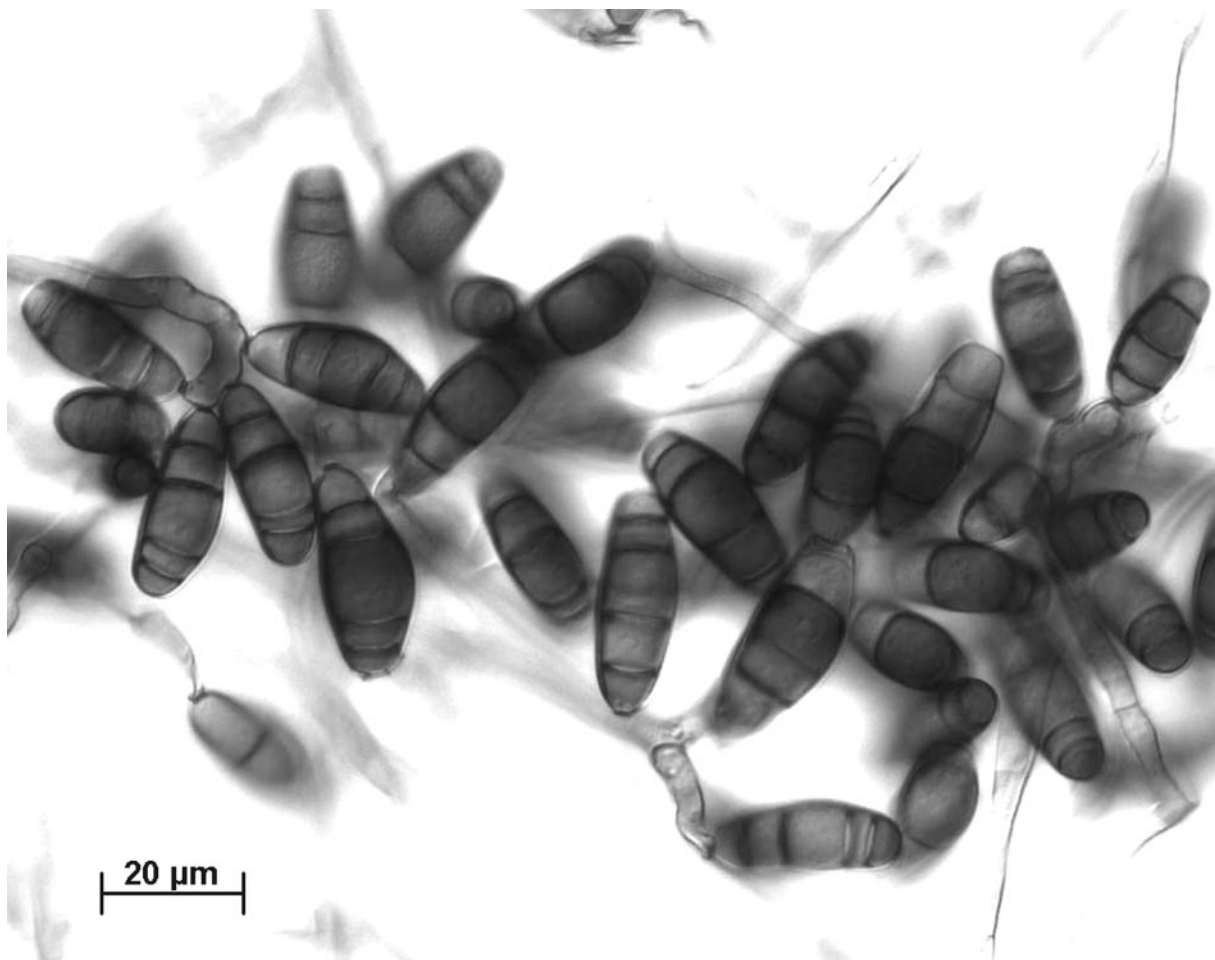
FIG. 2. *C. inaequalis* UAMH 10438 showing five-celled conidia that are straight to slightly curved.

sample, taken on the 9th day after admission, and microscopy revealed fungal hyphae. The WCC was $20,000 \times 10^6$/liter. At this point, i.p. fluconazole was commenced and then was changed to intravenous (i.v.) amphotericin B (45 mg/day) the next day. Fungal hyphae were also identified in four subsequent PD fluid samples. On March 24, 2004, the PD catheter was removed and a central venous catheter was placed for hemodialysis.

On day 16 after admission, the patient became febrile and tachycardic. Oxygen saturation was <85% on high-flow oxygen, and bibasal crepitations were heard upon auscultation. Blood gases indicated the presence of mixed metabolic and respiratory acidosis (pH, 7.19; O_2 pressure, 66 mm Hg; CO_2 pressure, 35.2 mm Hg; HCO_2 level, 13.2×10^6 mmol/liter), and the WCC was 38.4×10^6/liter. The patient died later that day due to respiratory failure.

Microbiology. Peritoneal fluid was collected and processed according to the normal laboratory protocol. A 50-ml sample of dialysate fluid was centrifuged (Labofuge GL, Heraeus Christ, Germany) at 3,000 rpm for 15 min, and the supernatant was removed. The deposit was then resuspended in 5 ml of normal saline and inoculated onto Columbia horse blood agar (Oxoid, Basingstoke, Hampshire, United Kingdom) incubated

at 35°C in 5% CO_2 and onto Sabouraud agar plates (Oxoid) incubated at 30°C. In addition, 3 ml of the deposit was inoculated into a BACTEC Peds Plus/F (Becton Dickinson, Sparks, MD) blood culture bottle and the bottle was incubated in a BACTEC 9240 incubator (Becton Dickinson) at 35°C. A Gram stain was made from the spun dialysate, and the cell count was determined for the noncentrifuged specimen.

No fungi were recovered from the primary culture plates. However, when the BACTEC 9240 signaled positive growth, fungal colonies were visually observed within the BACTEC Peds Plus/F bottles after Gram staining of a syringe-drawn sample revealed no bacterial organisms. The time to detection of positive growth ranged from 2 to 4 days. In each instance, a wet preparation confirmed the presence of hyphae. The fluid from these bottles was then subcultured on horse blood agar and Sabouraud agar plates incubated at 30°C. These plates grew colonies of a phaeoid fungus. The same fungus was isolated from five separate samples of PD fluid.

A microscopic mount from the colony on Sabouraud agar revealed septate, slightly curved, brown conidia borne singly on a geniculate conidiophore. The morphology was characteristic of species of the genus *Curvularia*, and identification as *Curvularia lunata* or *C. geniculata* was considered; however, the morphology and size of the conidia were not wholly typical of either species. One isolate (03-04) was therefore referred to

TABLE 1. Summary of details of seven cases of FP caused by *Curvularia* species

Year, reference	Patient's age (yrs), sex[a]	Identity of isolate	Time on PD	Preexisting condition(s)[b]	Presenting complaint(s)[c]	Locations of visible, dark fungal material	Signs of peritonism
1985, DeVault et al. (6)	60, F	*C. lunata*		PKD	Tenckhoff obstruction	Bag, catheter wall	No
1988, Brackett et al. (3)	46, M	*C. lunata*	2 yrs	DM	Black material in effluent fever	Bag, catheter, effluent	No
1989, Guarner et al. (12)	53, M	*Curvularia* species	1.5 yrs	DM, HTN, CHF	Abdo pain, fever, N/V, diarrhea	Catheter, effluent	Yes
1990, Ujhelyi et al. (20)	28, M	*Curvularia* species	1.5 yrs	MPGN	Abdo pain, black flakes in effluent	Bag, catheter	Yes
1994, Lopes et al. (15)	63, M	*C. lunata*	3 yrs	DM	Abdo pain, vomiting, fever, turbid effluent		Yes
2001, Canon et al. (4)	11, M	*Curvularia* species	9 mos	ICGN	Tenckhoff obstruction, cloudy dialysate	Catheter, transfer set	No
2005 (present case)	85, F	*C. inaequalis*	2 yrs	RVD	Abdo pain, turbid effluent		Yes

[a] F, female; M, male.
[b] PKD, polycystic kidney disease; DM, diabetes mellitus; HTN, hypertension; CHF, congestive heart; failure; MPGN, membranoproliferative glomerulonephropathy; ICGN, immune complex glomerulonephritis; RVD, renovascular disease.
[c] Abdo, abdominal; N/V, nausea and vomiting.
[d] N, neutrophils.
[e] Source of first direct microscopy sample positive for fungal hyphae.
[f] GNB, gram-negative bacillus; CoN, coagulase negative; *, organism was considered to be a contaminant.
[g] Total number of times isolated during separate admissions.
[h] RT, removal of Tenckhoff catheter; AMB, amphotericin B; 5FC, flucytosine.

the University of Alberta Microfungus Collection and Herbarium (UAMH), Edmonton, Canada, where it was deposited as UAMH 10438. The isolate was grown on potato dextrose agar (Difco Laboratories, Detroit, MI) and on tap water agar (1.8 g liter$^-$ of Difco agar). Conidia on tap water agar were five-celled (20) 24 to 36 by 9 to 13.5 μm (average, 28 by 11 μm) and smaller, slightly paler end cells. The conidia were only slightly curved (Fig. 1 and 2) and not geniculate as is *C. geniculata*. The distal cell was quite broadly rounded, and the basal cell was not, or only slightly, protuberant. The isolate was identified as *C. inaequalis* according to the key provided by Ellis (8). To confirm the phenotypic identification, sequencing of the internal transcribed spacer regions (ITS) of nuclear rRNA genes was performed. Procedures for DNA extraction, amplification, and sequencing followed the protocols outlined by Gibas et al. (10). A BLAST (1) search using the ITS sequence for this isolate showed it to be 99% similar (484 of 487 bases) to *C. inaequalis* AF120261 and 98% similar to *C. inaequalis* AF163081 (486 of 493 bases) and AF313409 (479 of 487 bases).

Discussion. Peritonitis is one of the most common and serious complications of PD, and most episodes are caused by staphylococci (11). Fungal peritonitis (FP) has a prevalence of 2% to 10.2%, with *Candida albicans* being the predominating etiologic agent. However, FP caused by filamentous fungi is much less common (2). The clinical signs of FP (abdominal pain accompanied by abdominal guarding, fever, and cloudy dialysate effluent) cannot differentiate the condition from bacterial peritonitis (7), but it is important to make an early differential diagnosis by microscopic examination and culture of the dialysate (2). FP is associated with higher rates of morbidity and mortality than bacterial infections, with FP mortality rates ranging from 5% to 25% (2). Risk factors for FP include recent exposure to antibiotics, immunosuppressive therapy, recent bacterial peritonitis, and the presence of bowel perforation (7, 20).

In our review of the literature, we found no other cases of clinical infection due to *C. inaequalis* and only six other cases of a *Curvularia* species complicating PD (Table 1) (3, 4, 6, 12, 15, 20). The mean age of the patient group was 49.4 ± 18.1 years (range, 11 to 85 years). The average time on dialysis was 21.5 ± 6.5 months (range, 9 to 36 months; $n = 6$). The preexisting causes of renal failure included diabetes mellitus ($n = 3$), glomerulonephropathy ($n = 2$), polycystic kidney disease ($n = 1$), and renovascular disease (present case). Six of the seven patients had had previous episodes of peritonitis. The presenting symptoms in these cases included clinical signs of peritonitis ($n = 4$), Tenckhoff catheter obstruction ($n = 2$), and abnormal effluent ($n = 5$). In five cases, black fungal material was grossly visible in the lumen of the Tenckhoff catheter. DeVault et al. (6) confirmed catheter wall invasion by histological examination of the catheter tubing; however, Guarner and coworkers (12) were not able to demonstrate tube invasion when they examined histologic sections. We did not find fungal material in the catheter. Antifungal therapy most frequently consisted of administration of i.v. amphotericin B ($n = 5$). Guarner et al. (12) administered i.v. flucytosine, and DeVault et al. (6) gave no antifungal treatment. Brackett et al. (3) initially used i.p. amphotericin B without success and changed to i.v. amphotericin B. In all cases, the dialysis catheter was ultimately removed. Catheter removal was a temporary measure in four cases. Ujhelyi et al. (20) and Lopes et al. (15) opted for their patients to remain on hemodialysis. In all the previous cases, the patients recovered and survived the acute episode. Our patient died despite receiving i.v. amphotericin therapy. *Curvularia* species have been shown to be susceptible in vitro to amphotericin B, itraconazole, and ketoconazole (13), and a favorable response to oral itraconazole has been reported in locally invasive phaeohyphomycosis (18).

The treatment of FP remains controversial. Microbiologic cures with amphotericin B, flucytosine, econazole, miconazole,

TABLE 1—Continued

PD fluid WCC (10⁶/liter) (% N)^d	Serum WCC (10⁶/liter) (% N)	Source of positive microscopy samples^e	Previous peritonitis	Catheter invasion	Coinfecting organism^f	No. of times *Curvularia* was isolated	Treatment^h	Outcome
2			Yes	Yes		1	RT for 2 wks	Infection resolved
1,474						3^g	i.p. AMB; cured with RT and i.v. AMB for 30 days	Infection resolved
49,600 (70)	10,700 (54)	Dark material	Yes	No	GNB	2^g	5FC for 5 days; RT for 25 days	Infection resolved
704 (51)	10,500 (62)	Dark material	Yes		*Proteus* species*	1	i.v. AMB (1.26 g total); RT	Infection resolved
Increased			Yes		*Staphylococcus aureus*	1	i.v. AMB (0.5 g total); RT	Infection resolved
7,075 (78)	7,000 (71)	Dark material	Yes		CoN *Staphylococcus* species*	1	i.v. AMB for 14 days; RT for 6 days	Infection resolved
2,328	15,100 (84)	Enrichment broth	Yes			5	i.v. AMB (270 mg total); RT	Patient died

and ketoconazole have been described (2, 7, 20). However, the dose of medication, the route and duration of treatment, and the use of combination antifungal therapy are debated. In addition to treatment with antifungals, catheter removal is believed to be essential for cure in cases of FP (2). However, controversy still exists on the best timing for catheter removal. The International Society of Peritoneal Dialysis recommends antifungal chemotherapy for 4 to 6 weeks and catheter removal if there is no clinical improvement after 4 to 7 days (21).

Three prior reports of *Curvularia* FP identified *C. lunata* as the species involved, and the remainder identified the fungus to the genus level only. This is the first report concerning *C. inaequalis*. *Curvularia* species are similar in colonial morphologies, appearing cottony to felty, raised, and brownish-gray to black. The conidiophores are typically pale brown to brown, erect, and simple or branched, producing conidia sympodially on a geniculate rachis. The *C. inaequalis* conidia are evenly colored or have end cells that are slightly paler, are predominantly straight or only slightly curved, and are mostly five-celled, with the central cell larger than the others (8, 19) (Fig. 1 and 2). The *C. lunata* conidia are similar in size (20 to 32 μm long and 9 to 15 μm wide) (8) to *C. inaequalis* conidia but differ in being predominantly four-celled and more strongly curved due to the swollen subterminal cell (5, 8, 19). Our isolate was confirmed to be *C. inaequalis* by morphology and high ITS sequence similarity. A molecular phylogenetic analysis of ITS sequences showed that *Cochliobolus* species, including anamorphs placed in the genera *Curvularia* and *Bipolaris*, form a monophyletic group and that *C. inaequalis* and *C. lunata* are distinct species (16).

C. inaequalis has a broad distribution in temperate and subtropical areas, and it is associated mainly with forage grasses and grains (19). Data from the Australian Plant Pest Database showed that three of the four strains listed were from plants in the family *Poaceae* in South Australia; the fourth strain was isolated from soil in Queensland. The species is reported to have been isolated from the air and dust of one Canadian home (14). How our patient acquired her infection is unknown. It is believed that she had not had any recent contact with soil. Two cases of *Curvularia* FP have been associated with documented gross environmental contamination. These in-

clude the case of a child who played in a wooded area (4) and that of a patient who would work in the garden prior to exchanges (20). These cases are consistent with the literature, which indicates that clinically relevant *Curvularia* disease is very often considered to be associated with soil contact. Cases include that of a football player (17) and those of gardeners and of children who played outdoors (9).

In conclusion, several important points arising from our review of *Curvularia* FP cases are that (i) pieces of dark material present in the effluent or catheter may indicate the presence of a phaeoid fungus and should be examined microscopically, (ii) removal of the PD catheter is a crucial element of treatment, and (iii) cure is achieved most frequently with i.v. antifungals, whereas the only trial of i.p. therapy failed. Distinguishing features in our case are the much older age of the patient (85 years), the lack of response to i.v. therapy and the fatal outcome, and the etiology attributed to *C. inaequalis*.

Nucleotide sequence accession number. The ITS sequence from the case isolate is deposited in GenBank under accession number AY941256.

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