NON-CANDIDAL FUNGAL PERITONITIS IN FAR NORTH QUEENSLAND: A CASE SERIES

Richard A. Baer, John P. Killen, Yeoungjee Cho, and Murty Mantha

Department of Renal Medicine, Cairns Base Hospital, Cairns, Australia

♦ **Background:** Fungal peritonitis is a recognized complication in patients with end-stage renal failure treated with peritoneal dialysis (PD). Most infections are attributable to *Candida* species. In approximately one third of cases, the causative fungus is a non-*Candida* species. Recent reports in the literature show a rising incidence of non-candidal fungal peritonitis (NCFP). We report a case series of NCFP, together with two hitherto unreported species of fungi causing peritonitis, from a tropical geographic area (Far North Queensland).

♦ **Methods:** This series of 10 cases of NCFP was identified from the PD peritonitis database in Far North Queensland between 1998 and 2010. All 10 patients were from the Aboriginal and Torres Strait Islander ethnic group, 8 of whom lived in remote locations. All but 1 patient had type 2 diabetes mellitus. Of the 10 cases, 7 occurred while the patients received continuous ambulatory PD. Only 1 patient avoided catheter removal, and 5 patients were permanently transferred to hemodialysis. No patient died as a result of the fungal infection. All 10 fungi represented different species. Most (6 of 10) were saprophytic; only 2 were normal skin flora. Two of the causative species (*Chaetomium* and *Beauveria*) have rarely been associated with any form of human infection. In 7 patients, the infection occurred during the wet season (November – April). All cases met clinical criteria for peritonitis.

♦ **Discussion and Conclusions:** The NCFP cases described in this series involved a variety of previously known fungal species and also two new species that have not been reported to cause disease in humans. Indigenous patients from Far North Queensland are particularly predisposed to infection with these exotic fungi as a result of environmental and social factors. Further understanding is desirable to help devise preventive strategies to avoid the consequences of catheter failure.

KEY WORDS: Fungal peritonitis; Aboriginal and Torres Strait Islanders; ATSI; indigenous; *Chaetomium*; *Beauveria*.

Fungal peritonitis constitutes up to 10% of all peritoneal dialysis (PD)-related peritonitis episodes and is more prominent in the tropical states of Australia (1). Its presentation is identical to that of bacterial peritonitis (2). Episodes are more likely to occur after a period of antibiotic use, although such use is not a prerequisite, and they may be related to yeasts rather than to filamentous organisms (3–6). Colonization with fungi is resistant to antifungal therapy alone, and therefore removal of the catheter together with antifungal treatment is now considered standard therapy (6). Permanent transfer to hemodialysis may result, and mortality rates are reported to range between 9% and 44% (3,6,7).

Peritonitis rates are known to be relatively high in the tropics because of the hot and humid environment, which favors fungal growth of increased virulence and diverse species (8,9). Rates of infection with unusual, and often otherwise nonpathogenic, fungi are increasing (2). Environmental moisture levels reflect the bimodal seasonal variation, with the wet season occurring during summer (November – April in our region), leading to an increased potential for fungal organisms to be identified.

In published case series of fungal peritonitis throughout the world, *Candida* species predominate. The reported incidence of non-candidal species was 8.5% in a series ending in 2000 (10), with a rising trend (17% – 40%) being evident in later series (7,11–15). Despite that increase, there is a paucity of data in the literature regarding the potential pathogenicity of these organisms in the tropical environment. The present case series describes 10 cases of PD-related non-candidal fungal peritonitis (NCFP) in which specific causative organisms have been isolated, some of which are new to the peritonitis literature.

Further knowledge of the causative organisms will help in a number of ways. Antifungal therapy should be

Perit Dial Int 2013; 33(5):559–564 www.PDIConnect.com
epub ahead of print: 01 July 2013 doi:10.3747/pdi.2012.00024

Correspondence to: R. Baer, Renal Department, Level 6
B Block, Cairns Base Hospital, Cairns 4870 Australia.

Richard_Baer@health.qld.gov.au

Received 7 February 2012; accepted 14 October 2012

individualized in NCFP (7). In PD peritonitis management, the common protocol is for fungal prophylaxis therapy to be given at the time of giving antibiotics for bacterial infections. The specific prophylaxis is chosen based on knowledge of local organisms. Guidance for the appropriate choice of empiric treatment is also important because fungi can be difficult to grow, and the lag period before samples become positive can be many days.

Patients living in remote settings are particularly affected if catheter removal becomes necessary as a result of fungal peritonitis. The catheter usually cannot be salvaged with antifungals, but instead must be removed (16). The patient then requires hemodialysis, and the advantages of PD are lost.

METHODS

All cases of PD-related peritonitis treated at Cairns Base Hospital during 1998 – 2010 were reviewed. A retrospective chart and pathology review was undertaken for episodes of NCFP. Approval was obtained from the local human research ethics committee.

RESULTS

Over the entire study period, 379 cases of peritonitis occurred in 184 patients. Between 2005 and 2010 (a representative period with the most complete data available), our area had an average peritonitis rate of 1 episode in 14.5 patient-months (0.83 episodes per patient-year). The overall Australian peritonitis rate was 1 episode in 20.7 patient-months (0.58 episodes per patient-year) for the same period (1).

Of all the peritonitis cases in this study from Far North Queensland, 31 (8.2%) were fungal. Among the fungal cases, 9 patients had 10 episodes of peritonitis (32%) caused by non-candidal fungi. The remaining fungal episodes were caused by *Candida albicans* or non-*albicans* species (68%). Tables 1 and 2 respectively describe the relevant attributes of the patients and the organisms in the NCFP episodes.

All patients fit the accepted criteria for a diagnosis of peritonitis (abdominal pain, cloudy peritoneal effluent, and elevated effluent white cell count). Effluent samples were consistent with peritonitis, containing $280 - 80\,000 \times 10^6/\text{L}$ white cells where counts were available. The proportion of polymorphonuclear cells exceeded 50% except in 1 episode (patient 4, episode 1), who had two separate episodes with different organisms (episodes 1 and 2). Each episode in the series involved a different fungal species (no species occurred in more than 1 episode). Isolation of the fungus was possible

from both PD effluent and the catheter tip specimen in all samples that were available for testing. In only 2 of the 10 episodes was sensitivity or minimal inhibitory concentration (MIC) data available (patient 4, episode 1, and patient 8).

Seven episodes occurred in the wet season (November – April), and three in the dry season (May – October). Most of the patients (7 of 9) were using continuous ambulatory PD; the others were using automated PD. Diabetes was the cause of end-stage renal failure in 8 of the 9 patients. Eight episodes occurred in a remote or very remote setting [defined according to the Accessibility/Remoteness Index of Australia (17)], most of which were in the Torres Strait Islands. Ethnicity as an Aboriginal or Torres Strait Islander (ATSI) was overrepresented at 100% in a background dialysis population that is approximately 60% ATSI.

The current literature suggests that a combination of antifungal treatment and catheter removal is required to limit mortality in fungal peritonitis (6). Management varies somewhat because of patient or physician preference. In this retrospective series, both treatments were applied in 5 episodes. Patient 8 was treated with fluconazole until catheter removal; the others received between 3 weeks and 3 months of standard-dose oral fluconazole or itraconazole. In only 1 patient (patient 3) was catheter removal not performed; to avoid hemodialysis, he refused removal. He was treated successfully with a 6-week course of oral itraconazole. The other 4 cases were successfully managed with catheter removal alone because all were clinically well at the time that the positive fungal culture was reported. No direct fatalities occurred as a result of the infections.

Permanent transfer to hemodialysis occurred in 5 episodes (50%). The only other complication potentially attributable to fungal peritonitis was that of recurrent sterile intra-abdominal fluid collections requiring intermittent drainage (patient 6). One patient experienced a second episode of NCFP after an interval of 9 months (patient 4, episodes 1 and 2). One patient (patient 7) was in fact able to remain dialysis-free for 19 months after removal of her catheter, suggesting that removal of the substantial systemic insult from the fungus led to some recovery of renal function.

DISCUSSION

In Far North Queensland, the PD prevalence rate is similar to the overall Australian rate, with 22% of dialysis patients using this home-based therapy (17). The population is spread over Cape York from Cardwell in the south, to Normanton in the west, and to the Torres

TABLE 1
Patient Details of Ten Episodes of Dialysis-Related Non-Candidal Fungal Peritonitis

Pt ID	Sex (M/F)	Age at infection (years)	ATSI	Year of culture	Cause of ESRF	Mode of dialysis	Location [ARIA class (17)]	Antifungals	Catheter Removal	Catheter Reinsertion	Permanent transfer to HD
1	F	60	Yes	2002	DN	CAPD	Atherton Tablelands (remote)	Itraconazole 3 months	Yes	No	Yes
2	F	40	Yes	1998	DN	CAPD	Cape York (very remote)	No	Yes	Day 27	No
3	M	60	Yes	2004	DN	CAPD	Cairns (accessible)	Itraconazole 6 weeks	No	No	No
4	M	55	Yes	2007	DN	APD	TSI (very remote)	No	Yes	Day 35	No
				2008	DN	APD	TSI (very remote)	No	Yes	No	Yes
5	M	48	Yes	1998	DN	CAPD	TSI (very remote)	Fluconazole 4 weeks	Yes	Day 68	No
6	F	42	Yes	1998	DN	CAPD	Cairns (accessible)	Fluconazole 3 weeks	Yes	No	Yes
7	F	55	Yes	2008	DN and diffuse proliferative GN	APD	TSI (very remote)	No	Yes	No	No ^a
8	F	55	Yes	1998	DN	CAPD	TSI (very remote)	Fluconazole before removal	Yes	No	Yes
9	F	62	Yes	1999	Unknown, pt not diabetic	CAPD	TSI (very remote)	Fluconazole 3 weeks	Yes	No	Yes

Pt = patient; M/F = male or female; ATSI = Aboriginal and Torres Strait Islander; ESRF = end-stage renal failure; ARIA = Accessibility/Remoteness Index of Australia; HD = hemodialysis; DN = diabetic nephropathy; CAPD = continuous ambulatory peritoneal dialysis; TSI = Torres Strait Islands; APD = automated peritoneal dialysis; GB = glomerulonephritis.

^a Recovered renal function.

Strait Islands in the north. Remoteness is defined by the Accessibility/Remoteness Index of Australia, which categorizes locations as very remote, remote, moderately accessible, accessible, or highly accessible based on road distance from a locality to the closest service centers (17). Most of Far North Queensland falls into the remote or very remote categories. A large proportion of the PD population is indigenous (52%). Patients who are ethnically ATSI have a known increased risk of fungal peritonitis (3).

Unpublished local data show that PD practices in Far North Queensland over the period of the present study (1998 – 2010) remained relatively consistent. Automated PD is used in 90% of patients, and fungal prophylaxis during antibacterial use was not standard until the last 1 – 2 years of that period. Compared with automated PD, continuous ambulatory PD was overrepresented in the present case series, possibly because of the increased requirement for catheter access in continuous ambulatory PD (8 times compared with 2 times daily). The

TABLE 2
Organism and Pathology Details of Ten Episodes of Dialysis-Related Non-Candidal Fungal Peritonitis

Pt ID	Organism Name	Type	Pathogenicity	Month of culture	Season ^a	Effluent		Sensitivities	Resistances	Site	
						WCC ($\times 10^6$ /L)	Poly-morphs (%)			Effluent	Catheter tip
1	<i>Trichosporon asahii</i>	Normal skin flora	Common superficial mycosis, opportunistic	Aug	Dry	NA	NA			Yes	Yes
2	<i>Trichosporon beigelii</i> ^b	Normal skin flora	Common superficial mycosis, opportunistic	Apr	Wet	600	NA			Yes	Yes
3	<i>Paecilomyces variotii</i>	Common environmental organism	Opportunistic	Dec	Wet	80 000	94			Yes	Not found
4	<i>Penicillium chrysogenum</i>	Common environmental organism	Opportunistic	Jul	Dry	280	42	MICs		Yes	Yes
	<i>Cunninghamella bertholletiae</i>	Saprophyte	Opportunistic—rare in temperate climate	Apr	Wet	500	90			Yes	No, but catheter removed
5	<i>Aspergillus flavus</i>	Saprophyte	Opportunistic	Dec	Wet	700	NA			Yes	Not found; found on vas cath tip later
6	<i>Aspergillus terreus</i>	Saprophyte	Opportunistic	Mar	Wet	3 000	80			Yes	Yes
7	<i>Acremonium</i> sp.	Saprophyte	Opportunistic	Mar	Wet	NA	NA			Yes	Yes
8	<i>Chaetomium</i> sp.	Saprophyte	2 Case reports of human infection	Jun	Dry	700	98	Amphotericin B, itraconazole, fluconazole	5 Fluorocytosine	Yes	Not found; found on vas cath tip later
9	<i>Beauveria</i> sp.	Saprophyte	Saprophytic contaminant, entomopathogenic	Apr	Wet	2 520	89			Yes	Tip not processed

Pt = patient; WCC = white cell count; NA = not available; MICs = minimal inhibitory concentrations; vas cath = vascular catheter.

^a Dry season = May–Oct; wet season = Nov–Apr.

^b Formerly *T. cutaneum* (*beigelii* nomenclature now obsolete—that is, these species are undifferentiated).

expected seasonal variation in peritonitis episodes was observed, with predominance in the wet season, suggesting that health carers should have a higher index of suspicion for the diagnosis during that season.

This series identified 10 fungal species other than *Candida* that caused peritonitis in our tropical environment. Most of the non-candidal fungi appear to be opportunistic species that ordinarily do not cause disease. However, in this cohort of relatively immunosuppressed patients (predominantly diabetic, with end-stage renal failure), these usually harmless fungi resulted in peritonitis. Diabetes is likely to be a major contributing factor, given its overrepresentation in this study. Further complications from these pathogens were uncommon, and death as a result was not encountered, despite suggestions in the literature that non-candidal fungal infections predict mortality (18).

The clinical impact of fungal peritonitis on individual patients on PD is dire. Catheter removal for patients living in remote areas in the tropics usually results in significant lifestyle disruption and psychosocial stress as a result of transfer to in-center hemodialysis.

Sensitivity patterns are better understood for *Candida* species because sensitivity testing is more commonly available and performed. Empiric data are available for other species, although specific sensitivity testing is suggested for individual cases (19). Nystatin prophylaxis during antibiotic use has been suggested to potentially limit *Candida* peritonitis rates (20,21). That approach is unlikely to apply to non-candidal organisms, which are mostly non-yeasts.

In most of the episodes reported here (6 of 10), the organisms were saprophytic; only 2 were normal skin flora: *Trichosporon* species (19). That finding suggests that the organisms introduced into the peritoneum are likely to have come from external sources rather than from the skin. *Trichosporon* species are known to cause common superficial mycosis, but can act in an opportunistic fashion to cause systemic disease. This opportunistic nature is also known for the other species found, except for those in patients 8 and 9: *Chaetomium* and *Beauveria*. Of the fungi found in the present series, those two are rarely associated with human infections (22,23). The present series includes the first reported cases of peritonitis attributable to those organisms. Further understanding of the organisms involved will help in adjusting prophylactic strategies to improve outcomes.

Fungal peritonitis is known to be more likely to occur after a course of an antibacterial agent (3), but previous antibiotics may not be necessary, as reported in a series by Rosa *et al.* (4), in which fungal peritonitis was

preceded by recent antibacterial use [preceding 3 months (6)] in only 1 of 5 cases. Antibiotic treatment preceded NCFP in 3 of our 10 cases, and it is unclear whether prophylactic antifungal therapy would have prevented those episodes.

CONCLUSIONS

This case series supports the need for more understanding of NCFP in PD patients. It also supports the background literature, in that infection with such fungi can cause substantial morbidity and is best treated with prompt catheter removal and aggressive antifungal therapy. Fungal peritonitis can be attributed to a wide variety of fungi apart from the more common yeast genus *Candida*. The biodiversity found in tropical regions such as Far North Queensland is likely to contribute to the breadth of variation in isolates. *Chaetomium* and *Beauveria* can be opportunistic pathogens and cause peritonitis in the diabetic PD population. This descriptive series will help to further clarify management and prevention strategies when considering guidelines with respect to antifungal prophylaxis and treatment and to making appropriate choices in a tropical location.

ACKNOWLEDGMENTS

Many thanks to CN Frank Grainer, who kindly formatted the PD database to enable case finding, and to CN Phil Wilson for data entry.

DISCLOSURES

All the authors declared no financial conflicts of interest.

REFERENCES

1. McDonald S, Hurst K, eds. *The 34th Annual ANZDATA Report 2011*. Adelaide, South Australia: Australia and New Zealand Dialysis and Transplant Registry; 2012.
2. Prasad N, Gupta A. Fungal peritonitis in peritoneal dialysis patients. *Perit Dial Int* 2005; 25:207–22.
3. Miles R, Hawley CM, McDonald SP, Brown FG, Rosman JB, Wiggins KJ, *et al.* Predictors and outcomes of fungal peritonitis in peritoneal dialysis patients. *Kidney Int* 2009; 76:622–8.
4. Rosa NG, Silva S, Lopes JA, Branco P, de Almeida E, Ribeiro C, *et al.* Fungal peritonitis in peritoneal dialysis patients: is previous antibiotic therapy an essential condition? *Mycoses* 2007; 50:79–81.
5. Predari SC, de Paulis AN, Verón D, Zucchini A, Santoianni JE. Fungal peritonitis in patients on peritoneal dialysis:

- twenty five years of experience in a teaching hospital in Argentina. *Rev Argent Microbiol* 2007; 39:213–17.
6. Piraino B, Bailie GR, Bernardini J, Boeschoten E, Gupta A, Holmes C, *et al.* Peritoneal dialysis-related infections recommendations: 2005 update. *Perit Dial Int* 2005; 25:107–31.
 7. Wang AY, Yu AW, Li PK, Lam PK, Leung CB, Lai KN, *et al.* Factors predicting outcome of fungal peritonitis in peritoneal dialysis: analysis of a 9-year experience of fungal peritonitis in a single center. *Am J Kidney Dis* 2000; 36:1183–92.
 8. Gow NA, Brown AJ, Odds FC. Fungal morphogenesis and host invasion. *Curr Opin Microbiol* 2002; 5:366–71.
 9. Alves FR, Dantas RC, Lugon JR. Higher incidence of catheter-related infections in a tropical climate. *Adv Perit Dial* 1993; 9:244–7.
 10. Bibashi E, Kokolina E, Sigler L, Sofianou D, Tsakiris D, Visvardis G, *et al.* Three cases of uncommon fungal peritonitis in patients undergoing peritoneal dialysis. *Perit Dial Int* 2002; 22:523–5.
 11. Unal A, Kocyigit I, Sipahioglu MH, Tokgoz B, Oymak O, Utas C. Fungal peritonitis in peritoneal dialysis: an analysis of 21 cases. *Int Urol Nephrol* 2011; 43:211–13.
 12. Indhumathi E, Chandrasekaran V, Jagadeswaran D, Varadarajan M, Abraham G, Soundararajan P. The risk factors and outcome of fungal peritonitis in continuous ambulatory peritoneal dialysis patients. *Indian J Med Microbiol* 2009; 27:59–61.
 13. Felgueiras J, del Peso G, Bajo A, Hevia C, Romero S, Celadilla O, *et al.* Risk of technique failure and death in fungal peritonitis is determined mainly by duration on peritoneal dialysis: single-center experience of 24 years. *Adv Perit Dial* 2006; 22:77–81.
 14. Das R, Vaux E, Barker L, Naik R. Fungal peritonitis complicating peritoneal dialysis: report of 18 cases and analysis of outcomes. *Adv Perit Dial* 2006; 22:55–9.
 15. Manzano-Gayosso P, Hernández-Hernández F, Méndez-Tovar LJ, González-Monroy J, López-Martínez R. Fungal peritonitis in 15 patients on continuous ambulatory peritoneal dialysis (CAPD). *Mycoses* 2003; 46:425–9.
 16. Chang TI, Kim HW, Park JT, Lee DH, Lee JH, Yoo TH, *et al.* Early catheter removal improves patient survival in peritoneal dialysis patients with fungal peritonitis: results of ninety-four episodes of fungal peritonitis at a single center. *Perit Dial Int* 2011; 31:60–6.
 17. Australia, Department of Health and Ageing. *Measuring Remoteness: Accessibility/Remoteness Index of Australia (ARIA)*. Rev. ed. Canberra, Australia: Government of Australia, Department of Health and Ageing; 2001.
 18. Ram R, Swarnalatha G, Neela P, Murty KV. Fungal peritonitis in patients on continuous ambulatory peritoneal dialysis: a single-centre experience in India. *Nephron Clin Pract* 2008; 110:c207–12.
 19. University of Adelaide. Clinical Groupings for Fungal Infections [Web page]. Adelaide, Australia: University of Adelaide; n.d. [Available at: <http://www.mycology.adelaide.edu.au/Mycoses/>; accessed 12 April 2013]
 20. The CARI guidelines. Evidence for peritonitis treatment and prophylaxis: treatment of peritoneal dialysis-associated fungal peritonitis. *Nephrology (Carlton)* 2004; 9(Suppl 3):S78–81.
 21. Lo WK, Chan CY, Cheng SW, Poon JF, Chan DT, Cheng IK. A prospective randomized control study of oral nystatin prophylaxis for *Candida* peritonitis complicating continuous ambulatory peritoneal dialysis. *Am J Kidney Dis* 1996; 28:549–52.
 22. Hubka V, Mencl K, Skorepova M, Lyskova P, Zalabska E. Phaeohyphomycosis and onychomycosis due to *Chaetomium* spp., including the first report of *Chaetomium brasiliense* infection. *Med Mycol* 2011; 49:724–33.
 23. Garcia Lozano T, Aznar Oroval E, Perez Ballesteros P, Lorente Alegre P. Isolation of *Beauveria bassiana* in a bronchoalveolar lavage specimen from a patient with bladder cancer [Spanish]. *Rev Iberoam Micol* 2011; 28:198–9.