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MAJOR ARTICLE

Cryptococcus Species Other Than *Cryptococcus neoformans* and *Cryptococcus gattii*: Are They Clinically Significant?

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Background. *Cryptococcus* spp is a major cause of opportunistic infections in immunocompromised patients, primarily due to *Cryptococcus neoformans* and *Cryptococcus gattii*. There are occasional reports of other *Cryptococcus* species causing invasive human disease. However, their epidemiology and clinical significance are not fully defined. We sought to describe cases with cultures positive for *Cryptococcus* species other than *C neoformans* and *C gattii*.

Methods. A retrospective descriptive analysis of clinical and laboratory data of patients with cultures growing *Cryptococcus* species other than *C neoformans* and *C gattii* from November 2011 to February 2019 was performed. Three Mayo Clinic sites in Arizona, Florida, and Minnesota were included.

Results. From 176 cases with a culture growing *Cryptococcus* spp, 54 patients (30%) had a culture for *Cryptococcus* other than *C neoformans* and *C gattii* in the study time frame. The most common species were *Cryptococcus magnus*, *Cryptococcus laurentii*, and *Cryptococcus ater*. The organisms were isolated and identified in culture of bronchoalveolar lavage (11), skin (11), urine (7), oral (4), sinus (3), intraoperative soft tissue (3), sputum (2), synovial fluid (2), cerebrospinal fluid (2), and intravenous catheter (2), among others (7).

Only 8 (15%) cases were considered to be potentially pathogenic, with 1 case of invasive disease. Antifungal treatment was fluconazole, itraconazole, and griseofulvin, for a mean systemic antifungal duration of 42 days.

Conclusions. This large series of patients with *Cryptococcus* spp other than *C neoformans* and *C gattii* suggests that these species rarely cause clinically significant infection in humans. Only 1 case of invasive disease was found.

Keywords. *Cryptococcus*; fungal infection; immunocompromised host; mycology; non-*neoformans*/*gattii*.

Cryptococcus species are ubiquitous, encapsulated yeasts found worldwide and are commonly associated with environmental exposures including pigeon droppings, soil, water, and certain foods [1]. This organism has become a significant pathogen, particularly since the onset of the human immunodeficiency virus (HIV) pandemic and the expanding numbers of immunocompromised populations, although it has also been described as pathogenic in immunocompetent hosts. Although most cryptococcal disease is caused by *Cryptococcus neoformans* and *Cryptococcus gattii*, there are increasing reports of infections attributed to species other than these 2 most prominent species. However, clinical information regarding human disease from these pathogens is largely restricted to sporadic case reports.

Cryptococcal infection other than *C neoformans* and *C gattii* is most commonly due to either *C laurentii* or *C albidus*, making up approximately 80% of cases [1, 2]. Infection has also been reported with *Cryptococcus diffluens*, *Cryptococcus liquefaciens*, *Cryptococcus uniguttulatus*, *Cryptococcus adeliensis*, *Cryptococcus luteolus*, and *Cryptococcus curvatus* [3–8]. The spectrum of disease appears to be similar to *C neoformans*, which most commonly affects the bloodstream or central nervous system [9]. Risk factors for infection with these organisms have included impaired cell-mediated immunity, specifically HIV/acquired immune deficiency syndrome (AIDS), and presence of an invasive catheter [9]. Furthermore, *C diffluens* and *C liquefaciens* may play a role in atopic dermatitis [10, 11], whereas *C albidus* has been implicated in the pathogenesis of summer-type hypersensitivity pneumonitis [12].

The diagnosis of non-*C neoformans* and non-*C gattii* *Cryptococcus* species is challenging, particularly with poor sensitivity of antigen testing compared with the more traditional *Cryptococcus* species [2, 9]. However, species differentiation is important because these organisms have been reported to have relatively high resistance to azoles and flucytosine—the standard regimen for *C neoformans* and *C gattii* [13]. Complicating matters further, these organisms are common colonizers of the respiratory and gastrointestinal tracts [2, 9, 14]. As it stands, there is little to guide clinicians regarding the clinical significance of a culture growing a *Cryptococcus* species other than *C neoformans* and *C gattii*.

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METHODS

We conducted a retrospective, electronic medical record review of patients with a culture positive for a *Cryptococcus* species other than *neoformans* or *gattii* between November 2011 and February 2019. Culture results were identified by review of our institution's internal culture registry, including sites in Arizona, Florida, and Minnesota. We included patients who had a culture from any source reported positive for any *Cryptococcus* species and restricted the analysis only to cases identified as species other than *C neoformans* or *C gattii*.

Collected data included demographics such as age and sex. Clinical data included symptoms, diagnosis, reason for culture, comorbidities including diabetes mellitus, chronic kidney disease (stages III/IV), end-stage renal disease, chronic obstructive pulmonary disease, current malignancy, cirrhosis, HIV/AIDS, and organ transplant, and current immunosuppression at the time of diagnosis. Laboratory data included culture collection date, sample source, culture results, cryptococcal antigen test results, and antifungal susceptibilities when available.

Cerebrospinal fluid, bone marrow aspirates, bone biopsies, intraoperative cultures from deep sources, synovial fluid, and blood were considered sterile sources. All other sources including skin/scalp swab cultures, bronchoalveolar lavage, urine culture, toenail culture, corneal cultures, mouth, and upper respiratory sources were considered nonsterile sources. Species identification was performed with either deoxyribonucleic acid sequencing or mass spectrometry.

Pathogenic cases were defined as presence of concurrent clinical symptoms, either local or disseminated, and absence of a reasonable alternative diagnosis based on clinical and further laboratory data such as presence of other known pathogens. Invasive fungal infection was defined as recovery of a fungal organism from a typically sterile site or detection of cryptococcal antigen from cerebrospinal fluid or blood, according to recent international guidelines [15].

Patient Consent Statement

This work was approved by the Institutional Review Board (IRB) at Mayo Clinic and was deemed exempt from revision (IRB no. 19-001020).

RESULTS

A total of 54 cultures positive for *Cryptococcus* other than *C neoformans* and *C gattii* were identified. The identified species include unspecified *C* non-*neoformans*/*gattii* (9), *Cryptococcus magnus* (9), *C laurentii* (8), *Cryptococcus ater* (7), *C albidus* (6), *C uniguttulatus* (5), *C liquefaciens* (4), *C diffluens* (3), *Cryptococcus albidosimilis* (1), *Cryptococcus randhawii* (1), and *Cryptococcus flavescens* (1). Cultured specimen and sites included bronchoalveolar lavage (11), skin (11), urine (7), oral (4), sinus (3), intraoperative soft tissue (3), sputum (2), synovial fluid (2), cerebrospinal fluid (2), intravenous catheter (2), intervertebral disk (1), bone marrow aspirate (1), cornea (1), donor liver preservation fluid (1), external ear (1), toe nail (1), and peritoneal fluid (1).

A total of 8 isolates were determined to be potentially pathogenic based on predefined criteria (or as assessed by the treating provider). Baseline characteristics and comorbidities between the 2 groups are described in Table 1 and culture sites are listed in Table 2. Pathogenic organisms included *C laurentii* (4), *C liquifaciens* (2), *C magnus* (2), and *C albidosimilis* (1). These isolates are further described in Table 3. Serum cryptococcal antigen was collected only in 2 and 8 cases of pathogenic and non-pathogenic infections, respectively. Cerebrospinal fluid cryptococcal antigen was collected in 1 pathogenic case and 0 non-pathogenic cases. All cryptococcal antigen testing was negative.

Table 1. Group-Level Characteristics of Pathogenic and Non-Pathogenic Isolates

Characteristics	Pathogenic (8)	Non-Pathogenic (46)	Total (54)
Age (years)	36.6[a]	55.5[a]	52.7[a]
Gender (male)	7 (87.5%)	26 (56.5%)	33 (61.1%)
Immunosuppression	1 (12.5%)	12 (26.1%)	11 (20.4%)
Diabetes mellitus	0 (0%)	13 (28.3%)	13 (24.1%)
Corticosteroids	0 (0%)	14 (30.1%)	14 (25.9%)
Transplant	0 (0%)	6 (13.0%)	6 (11.1%)
Cirrhosis	1 (12.5%)	4 (8.7%)	5 (9.3%)
Active malignancy	0 (0%)	3 (6.5%)	3 (5.6%)
COPD	1 (12.5%)	2 (4.3%)	3 (5.6%)
CKD3/4	0 (0%)	2 (4.3%)	2 (3.7%)
ESRD	0 (0%)	2 (4.3%)	2 (3.7%)
HIV/AIDS	0 (0%)	0 (0%)	0 (0%)

Abbreviations: AIDS, acquired immunodeficiency syndrome; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HIV, human immunodeficiency virus.

[a]Mean value.

Table 2. Culture Sites Positive for *Cryptococcus* Species Other Than *Cryptococcus neoformans* and *Cryptococcus gattii*

Culture Sites	Pathogenic	Non-Pathogenic
Bone marrow	0	1
Bronchoalveolar lavage	0	11
Cerebrospinal fluid	0	2
Cornea	0	1
Donor liver blood vessel preservation fluid	0	1
External ear	1	0
Intervertebral disk	0	1
Intraoperative soft tissue	0	3
Intravenous catheter	1	1
Oral	1	3
Peritoneal fluid	1	0
Sinus	0	3
Skin	2	9
Sputum	0	2
Synovial fluid	1	1
Toe nail	1	0
Urine	0	7

Pathogenic sites of infection include skin (2), mouth (1), toe nail (1), intravenous catheter (1), peritoneal fluid (1), synovial fluid (1), and external ear (1). Six of these were part of a polymicrobial infection with non-*Cryptococcus* organisms. Only 1 of these cases, the peritoneal fluid isolate, was an invasive infection from primary peritonitis that was not polymicrobial. Six of these cases were treated with antifungal medication, including oral fluconazole (3), topical fluconazole (1), itraconazole (1), and griseofulvin (1). The invasive case was successfully treated with oral fluconazole for 28 days. Systemic antifungals were administered for a mean of 42 days (range, 14–84 days). The remaining 2 pathogenic cases were treated with either acetic acid wraps or tunneled intravenous catheter removal alone. Six non-pathogenic cases received antifungal medications active against *Cryptococcus* for other indications. One patient was preemptively treated when their donor's liver preservation fluid culture grew *C magnus* after transplantation and received 120 days of fluconazole without developing cryptococcosis. Only 2 isolates underwent successful antifungal susceptibility testing: 1 pathogenic *C laurentii* from a toe nail culture and 1 non-pathogenic *C uniguttulatus* from a urine culture. The susceptibility results are listed in Table 4. Three further isolates were tested but did not grow on susceptibility media. There were no cases of hypersensitivity pneumonitis in patients with a culture growing *C albidus*. Non-pathogenic isolates are detailed in Supplementary Table 1.

All patients with non-*cryptococcus*, non-*gattii Cryptococcus* infection responded to treatment. 6-month mortality was 0% in the pathogenic group and 11% (5 patients) in the non-pathogenic group. Mortality in the non-pathogenic group was due to unrelated causes in 4 patients, and unknown in one patient. One patient with a pathogenic culture result did not have 6-month follow-up, compared with 7 in the non-pathogenic group.

DISCUSSION

Clinically significant disease caused by *Cryptococcus* other than *C neoformans* or *C gattii* is rare. This study showed only 8 pathogenic cultures, only 1 of which represented an invasive infection affecting the peritoneum. Although *C laurentii* has been reported to cause peritonitis in patients with peritoneal dialysis [16], our case of peritonitis was not in a dialysis patient. Most infections were mild, including skin infection, stomatitis, and onychomycosis. Pathogenic organisms were largely *C laurentii*, which is consistent with past studies [1, 2]. There were also no positive cryptococcal antigens, which could be due to the overall low morbidity of cases or poor sensitivity in these non-*neoformans*/non-*gattii* organisms.

The pathogenic and non-pathogenic groups differed in their culture sources. There were no pathogenic cultures of the urine or respiratory tract. There were also no cases of fungemia, although there was 1 infected intravenous catheter without growth of *Cryptococcus* on peripheral blood culture. The only cultures of cerebrospinal fluid cornea were non-pathogenic, although pathogenic cases have been reported [7, 17–21]. Furthermore, cultures of intervertebral disk, bone marrow aspirate, and sinus were all non-pathogenic, although in small numbers. We did have numerous pathogenic and non-pathogenic skin cultures, which is also consistent with past reports [11,

Table 3. Pathogenic Isolates of *Cryptococcus* species Other Than *Cryptococcus neoformans* and *Cryptococcus gattii*

Species	Age	Gender	Site	Clinical Syndrome	Comorbidity	Treatment	Duration (Days)
Cryptococcus albidosimilis	54	M	Peritoneal fluid	Peritonitis	Cirrhosis, COPD	Fluconazole	28
Cryptococcus laurentii	19	F	Toe nail	Onychomycosis	None	Itraconazole	84
C laurentii	21	M	Skin	Folliculitis decalvans	None	Acetic acid	60
C laurentii	11	M	Synovial fluid	Septic arthritis	None	Fluconazole	14
C laurentii	54	M	Mouth	Stomatitis	None	Fluconazole	84
Cryptococcus liquifaciens	64	M	Tunneled intravenous catheter	Intravenous catheter infection	TPN dependency	Catheter removal	N/A
C liquifaciens	61	M	Ear	Otitis externa	None	Topical fluconazole	30
Cryptococcus magnus	9	M	Skin	Folliculitis	None	Griseofulvin	42

Abbreviations: COPD, chronic obstructive pulmonary disease; f, female; m, male; N/A, not applicable; TPN, total parenteral nutrition.

Table 4. Antifungal Susceptibilities[a] of Two Isolates of *Cryptococcus* Species Other Than *Cryptococcus neoformans* and *Cryptococcus gattii*

Species	Amphotericin B	Caspofungin	Fluconazole	5-Flucytosine	Itraconazole	Voriconazole	Posaconazole
Cryptococcus laurentii	0.5	8	N/A	64	0.25	0.5	0.5
Cryptococcus uniguttulatus	1	0.12	32	≤0.06	1	0.5	2

Abbreviations: N/A, not applicable.

[a]Units: μg/mL.

22–24]. This review also did not note any pathogenic cultures of *C albidus*, *C ater*, *C diffluens*, or *C uniguttulatus*.

There were some important differences in characteristics between the pathogenic and non-pathogenic cultures worth noting. The pathogenic group tended to be younger (36.6 versus 55.5 years) and male (87.5% versus 56.5%). The pathogenic group had less comorbidity, specifically not including patients with diabetes mellitus, corticosteroid use, transplantation, active malignancy, or significant renal impairment. This may be a reflection of the noninvasive nature of the described cases.

Limitations of this study include its retrospective nature and only inclusion of centers that are part of the same enterprise health system. There were also no people with HIV, limiting applicability to this population. Given the relative rarity of these organisms, the overall numbers found were low, which limits the ability to draw final conclusions. This was particularly true with the available susceptibility data, where only 2 isolates successfully underwent susceptibility testing. Finally, a plurality of cultures was not identified past *Cryptococcus* other than *neoformans* and *gattii*. This limits a full assessment of the epidemiology of these cultures to a species level.

CONCLUSIONS

In conclusion, this study showed a low rate of clinical relevance to cultures growing *Cryptococcus* species other than *C neoformans* and *C gattii*. There was 1 case of invasive disease, in addition to the multiple reports available in the literature. However, cases in our description were overwhelmingly contaminants, colonizers, or mild infection. In addition, some sites did not yield any cases of true infection, including 2 of the 3 most common sites of respiratory and urinary cultures. Although *Cryptococcus* species other than *C neoformans* and *C gattii* have the potential to cause clinically significant infection, alternative causes should be evaluated in the appropriate clinical context.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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References

1. Miceli MH, Díaz JA, Lee SA. Emerging opportunistic yeast infections. Lancet Infect Dis **2011**; 11:142–51.
2. McCurdy LH, Morrow JD. Infections due to non-*neoformans* cryptococcal species. Compr Ther **2003**; 29:95–101.
3. Dromer F, Moulignier A, Dupont B, et al. Myeloradiculitis due to *Cryptococcus curvatus* in AIDS. AIDS **1995**; 9:395–6.
4. Rimek D, Haase G, Lück A, et al. First report of a case of meningitis caused by *Cryptococcus adeliensis* in a patient with acute myeloid leukemia. J Clin Microbiol **2004**; 42:481–3.
5. Animalu C, Mazumder S, Cleveland KO, Gelfand MS. *Cryptococcus uniguttulatus* meningitis. Am J Med Sci **2015**; 350:421–2.
6. Takemura H, Ohno H, Miura I, et al. The first reported case of central venous catheter-related fungemia caused by *Cryptococcus liquefaciens*. J Infect Chemother **2015**; 21:392–4.
7. Conde-Pereira C, Rodas-Rodríguez L, Díaz-Paz M, et al. Fatal case of polymicrobial meningitis caused by *Cryptococcus liquefaciens* and *Mycobacterium tuberculosis* complex in a human immunodeficiency virus-infected patient. J Clin Microbiol **2015**; 53:2753–5.
8. Hunter-Ellul L, Schepp ED, Lea A, Wilkerson MG. A rare case of *Cryptococcus luteolus*-related tenosynovitis. Infection **2014**; 42:771–4.
9. Khawcharoenporn T, Apisarnthanarak A, Mundy LM. Non-*neoformans* cryptococcal infections: a systematic review. Infection **2007**; 35:51–8.
10. Kato H, Sugita T, Ishibashi Y, Nishikawa A. Evaluation of the levels of specific IgE against *Cryptococcus diffluens* and *Cryptococcus liquefaciens* in patients with atopic dermatitis. Microbiol Immunol **2007**; 51:945–50.
11. Sugita T, Saito M, Ito T, et al. The basidiomycetous yeasts *Cryptococcus diffluens* and *C. liquefaciens* colonize the skin of patients with atopic dermatitis. Microbiol Immunol **2003**; 47:945–50.
12. Miyagawa T, Hamagami S, Tanigawa N. *Cryptococcus albidus*-induced summer-type hypersensitivity pneumonitis. Am J Respir Crit Care Med **2000**; 161:961–6.
13. Bernal-Martinez L, Gomez-Lopez A, Castelli MV, et al. Susceptibility profile of clinical isolates of non-*Cryptococcus neoformans*/non-*Cryptococcus gattii Cryptococcus* species and literature review. Med Mycol **2010**; 48:90–6.
14. Bauters TG, Swinne D, Boekhout T, et al. Repeated isolation of *Cryptococcus laurentii* from the oropharynx of an immunocompromized patient. Mycopathologia **2002**; 153:133–5.
15. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis **2020**; 71:1367–76.
16. Asano M, Mizutani M, Nagahara Y, et al. Successful treatment of *Cryptococcus laurentii* peritonitis in a patient on peritoneal dialysis. Intern Med **2015**; 54:941–4.
17. Liu Y, Ma S, Wang X, et al. *Cryptococcus albidus* encephalitis in newly diagnosed HIV-patient and literature review. Med Mycol Case Rep **2014**; 3:8–10.
18. Smith N, Sehring M, Chambers J, Patel P. Perspectives on non-*neoformans* cryptococcal opportunistic infections. J Community Hosp Intern Med Perspect **2017**; 7:214–7.
19. Fernández De Castro LE, Al Sarraf O, Lally JM, et al. *Cryptococcus albidus* keratitis after corneal transplantation. Cornea **2005**; 24:882–3.
20. Ritterband DC, Seedor JA, Shah MK, et al. A unique case of *Cryptococcus laurentii* keratitis spread by a rigid gas permeable contact lens in a patient with onychomycosis. Cornea **1998**; 17:115–8.
21. Huang YH, Lin IH, Chang TC, Tseng SH. Early diagnosis and successful treatment of *Cryptococcus albidus* keratitis. Medicine **2015**; 94:e885.
22. Gyimesi A, Bátor A, Görög P, et al. Cutaneous *Cryptococcus albidus* infection. Int J Dermatol **2017**; 56:452–4.
23. Molina-Leyva A, Ruiz-Carrascosa JC, Leyva-Garcia A, Husein-Elahmed H. Cutaneous *Cryptococcus laurentii* infection in an immunocompetent child. Int J Infect Dis **2013**; 17:e1232–3.
24. Hoang JK, Burruss J. Localized cutaneous *Cryptococcus albidus* infection in a 14-year-old boy on etanercept therapy. Pediatr Dermatol **2007**; 24:285–8.