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 opportunist 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 cryptoccocal 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 fluconosine—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.
METHODS

We conducted a retrospective, electronic medical record re-
view 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 pa-
tients 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 dis-
ease (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 in-
cluding skin/scalp swab cultures, bronchoalveolar lavage, urine
culture, toenail culture, corneal cultures, mouth, and upper res-
piratory 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 clin-
ical 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 or-
ganism 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 albidas
(6), C uniguttulatus (5), C liquefaciens (4), C diffluens (3),
Cryptococcus albidosimilis (1), Cryptococcus randhawii (1), and
Cryptococcus flavesens (1). Cultured specimen and sites in-
cluded 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), inter-
vertebral 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 patho-
genic 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
liquefaciens (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*         | 55.5*               | 52.7*      |
| 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 immu-
nodeficiency virus.

*Mean value.
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 blood vessel preservation fluid culture grew Cryptococcus 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 albidosimilis. 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, 22].

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                 | Osteomyelitis               | 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          | 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.
Cryptococcus laurentii
Cryptococcus 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 copylefted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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