REVIEW ARTICLE

Cryptococcosis in Solid-Organ, Hematopoietic Stem Cell, and Tissue Transplant Recipients: Evidence-Based Evolving Trends

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The impact of current transplantation practices on the characteristics of cryptococcosis in solid-organ transplant recipients is not well defined. The incidence of cryptococcal disease among solid-organ transplant recipients has remained unchanged; however, patients are less likely to present with central nervous system or disseminated disease and are more likely to have cryptococcosis limited to the lungs. Additionally, lipid formulations of amphotericin B are now used more frequently, whereas their use in combination with flucytosine has decreased. The overall mortality of cryptococcosis has significantly improved in the current era. Renal failure remains associated with poor outcome, whereas use of lipid formulations of amphotericin B is associated with a higher survival rate. Despite rare infectious complication, certain peculiar attributes of cryptococcal disease in hematopoietic stem cell recipients and tissue transplant recipients warrant recognition.

Cryptococcosis is a significant opportunistic infection in solid-organ transplant (SOT) recipients. The existing knowledge base about cryptococcal disease in SOT recipients has been accrued largely on the basis of case series that were reported as many as 2–3 decades ago. On the basis of these case series, the overall incidence of cryptococcosis in SOT recipients is ~2.8% (range, 0.3%–5%), and mortality rates are typically in the range 33%–42% [1, 2]. Organ transplantation, however, is a rapidly evolving field, and new developments abound, including advances in immunosuppression and improvements in transplantation practices. Although these trends have had a discernible effect on the epidemiology of a number of opportunistic infections [3–5], currently their impact on cryptococcosis in SOT recipients is less clear.

Unlike in SOT recipients, cryptococcal disease appears to be distinctly unusual in hematopoietic stem cell transplant (HSCT) recipients [1, 6]. Cryptococcosis has also been reported in tissue transplant recipients [7–11]. However, cryptococcal disease in these non-SOT recipients remains a poorly described entity. The goals of this review were to determine whether the characteristics of cryptococcal disease in SOT recipients have evolved in the current era and to summarize the clinical characteristics of cryptococcosis in HSCT and tissue transplant recipients.

METHODS

SOT, HSCT, and tissue allograft recipients (i.e., osteochondral, cardiac, vascular, cutaneous, corneal, and composite tissue allograft transplant recipients) with cryptococcosis were identified with a search of the PubMed database from the 1950s to August 2008 by cross-referencing the keywords "cryptococcosis" or "*Cryptococcus*" and "transplantation," "transplant," "keratoplasty," or "allograft." Reference lists of original articles were reviewed for additional cases. We previously summarized the world literature on cryptococcosis in SOT recipients through the 1990s [1]. For the purposes of this article, these case patients, hereafter referred to as the "prior cohort," were compared with

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Table 1. Incidence of cryptococcosis among solid-organ transplant recipients.

Variable [references[a]]	Incidence, %			*P*
	Median	Range	IQR	
Current cohort [13, 28, 49, 66, 78, 79]	1.56	0.45–4.1	0.57–4.1	.18[b]
Prior cohort [1, 24, 47, 57, 62, 73, 77, 80–88]	1.52	0.27–5.3	1.1–2.9	
Tacrolimus-based regimen [1, 23, 28, 53, 78]	1.67	0.52–4.6	1.1–4.1	.60[c]
Cyclosporine A–based regimen [24, 44, 47, 62, 84]	1.31	0.65–2.8	0.75–2.5	
CNI regimen [1, 23, 24, 28, 44, 47, 53, 62, 78, 84]	1.49	0.52–4.6	0.75–2.7	.063[d]
Non-CNI regimen [81, 85–87]	3.20	1.5–5.3	2.01–4.6	
T cell–depleting agent[e] [13, 49, 66]	2.04	0.64–2.48	0.64–2.48	
Living donor[f] [13, 23]	NA[f]	NA	NA	

NOTE. CNI, calcineurin inhibitor; IQR, interquartile range; NA, not available.

[a] References represent the studies from which the incidence was derived. Incidence was calculated on the basis of articles in which data on the numerator (i.e., the number of solid-organ transplant recipients who developed cryptococcosis) and the denominator (i.e., the total number of solid-organ transplant recipients) were explicitly provided.

[b] *P* value represents the comparison of incidence between current and prior cohorts.

[c] *P* value represents the comparison of incidence between solid-organ transplant recipients receiving a tacrolimus-based treatment regimen and those receiving a cyclosporine A–based treatment regimen.

[d] *P* value represents the comparison of incidence between solid-organ transplant recipients receiving a CNI treatment regimen and those receiving a non-CNI treatment regimen (including azathioprine, mycophenolate mofetil, or prednisone).

[e] Includes alemtuzumab or antithymocyte globulin.

[f] The median incidence in one study was 0 (0 of 15 patients), and the median incidence in the other study was 1.67 (3 of 180 patients). The range, IQR, and *P* value were not calculated for this variable, because only 2 articles provided the required data.

SOT recipients with cryptococcosis since 2001, hereafter referred to as the "current cohort."

Cryptococcosis was defined per the criteria proposed by the European Organization for Research and Treatment of Cancer–Mycosis Study Group [12]. The organ sites involved were classified as central nervous system (CNS), pulmonary, skin or soft tissue, and osteoarticular. Disseminated disease was defined as CNS disease or fungemia or involvement of $\geq$2 noncontiguous organ sites. The antifungal therapy used was referred to the initial or induction therapy.

Statistical analyses. Intercooled Stata, version 9.2 (StataCorp), was used for statistical analyses. Categorical data were compared between the 2 cohorts by using the χ^2 test. Continuous variables were compared using a rank-sum or Student's *t* test. The effects of multiple factors on outcome were estimated using a logistic model. All-cause death was the dependent variable, and explanatory variables were those previously found to be associated with outcome. A dichotomized variable for era (1950–2000 vs. 2001–2008) was then added to the final model to assess the effect of era on outcome.

RESULTS

SOT recipients. A total of 507 SOT recipients with cryptococcosis were identified; these included 187 case patients in the prior cohort and 320 in the current cohort [1, 13–78]. Based on articles in which data on the numerator (i.e., the number of recipients who developed cryptococcosis) and the denominator (i.e., the total number of SOT recipients) were explicitly provided, the overall median incidence of cryptococcosis was 1.52% (range, 0.27%–5.3%) in the prior cohort and 1.56% (range, 0.45%–4.1%) in the current cohort ($P = .18$) (table 1).

Characteristics of SOT recipients with cryptococcosis. The demographic and clinical characteristics of the 2 cohorts are presented in table 2. Patients in the current cohort were older, and 9 of them were recipients of living donor allografts. Compared with the prior cohort, patients in the current cohort were more likely to be lung or multivisceral transplant recipients (table 2). There were proportionately fewer renal transplant recipients in the current cohort than in the prior cohort (table 2). In the current cohort, tacrolimus was used more frequently for treatment (64% vs. 10%; $P < .001$), whereas a regimen not based on calcineurin inhibitors was prescribed less often (10% vs. 67%; $P < .001$). Compared with the prior cohort, fewer patients in the current cohort had renal failure at baseline; however, no differences existed in other demographic or clinical characteristics between the 2 cohorts (table 2).

Characteristics of cryptococcal disease. Time to onset of cryptococcosis after transplantation was similar in the 2 cohorts (table 3). However, several notable differences were observed in the clinical presentation of cryptococcal disease in the 2 cohorts. Patients in the current cohort were less likely to present with CNS, skin, soft-tissue, or osteoarticular disease and disseminated cryptococcosis but were more likely to have pul-

Table 2. Demographic and clinical characteristics of solid-organ transplant recipients with cryptococcosis in the prior and current cohorts.

Characteristic	Prior cohort (1950–2000)	Current cohort (2001–2008)	*P*
Total no. of patients	187	320	
Age, median years (n = 220)	45	53	<.001
Male sex (n = 222)	68	66	.8
Type of transplant			
Kidney (n = 223)	76	59	.037
Liver (n = 54)	18	16	.60
Heart (n = 21)	4	9	.05
Lung (n = 15)	2	7	.03
Other or multivisceral (n = 13)	<1	9	<.001
Kidney and pancreas	<1	6	.005
Kidney and heart	<1	1	.13
Small bowel and pancreas	<1	1	.28
Living donor (n = 9)	NA	2.8	
Immunosuppressive regimen			
Tacrolimus based (n = 107)	10	64	<.001
Cyclosporine A based (n = 45)	19	17	.68
Other[a] (n = 60)	67	10	<.001
Retransplantation (n = 22)	20	13	.26
Prior rejection (n = 52)	28.1	27.6	.94
Renal failure at baseline (n = 64)	69.6	30.8	<.001

NOTE. Data are percentage of patients, unless otherwise indicated. *n,* number of case patients with data available; NA, not available.

[a] Other regimens included 55 with azathioprine, 4 with mycophenolate mofetil and prednisone, and 1 with mycophenolate mofetil and rapamycin, among 60 case patients with data available.

monary cryptococcosis and to have disease limited to the lungs than were patients in the prior cohort (table 3).

Overall, the use of amphotericin B (AmB) deoxycholate decreased, whereas the use of lipid formulations of AmB and fluconazole increased in the current cohort (table 3). Concurrent use of flucytosine decreased in the current cohort (table 3). However, further analysis showed that this decrease was mainly because of less frequent use of flucytosine when lipid formulations of AmB were prescribed (28% vs. 67%; P = .049), whereas the frequency of concurrent use of flucytosine with AmB deoxycholate or with fluconazole was similar for the 2 cohorts (table 3).

When antifungal treatment practices were stratified by the site of infection, we found that patients with CNS disease in the current cohort were more likely to be treated with lipid formulations of AmB (50% vs. 3%; P < .001) and were less likely to be treated with AmB deoxycholate than were patients in the prior cohort (table 3). Similarly, concurrent use of flucytosine as induction therapy for CNS disease decreased significantly in the current cohort (table 3). For patients with cryptococcal disease limited to the lungs, lipid formulations of AmB and fluconazole were prescribed more frequently in the current cohort, whereas AmB deoxycholate was used less often (table 3).

Of a total of 64 SOT recipients for whom lipid formulations of AmB were used, 21 received liposomal AmB, 38 received AmB lipid complex, and 5 received an unspecified lipid formulation. However, the dosage of liposomal AmB was available for only 5 patients (3, 3, and 4 mg/kg/day and 50 and 210 mg/day); the duration of treatment was available for 13 patients (median, 3 weeks; interquartile range, 3–5 weeks). The dosage of AmB lipid complex was available for only 1 patient (400 mg/day), and the duration of treatment was available for 25 patients (median, 3 weeks; interquartile range, 2–5.4 weeks).

Outcome. The overall mortality rate for cryptococcosis was lower in the current cohort than in the prior cohort (19.6% vs. 39.9%; P < .001) (table 4). When stratified by the site of infection, the mortality associated with CNS infection (30% vs. 51%; P < .001) and disseminated disease (31% vs. 50%; P = .001) improved substantially in the current cohort, whereas no changes were documented in the mortality of pulmonary, skin, soft-tissue, or osteoarticular disease in the 2 cohorts. Patients receiving tacrolimus treatment in the current cohort had a lower mortality than did those in the prior cohort (9% vs. 38%;

Table 3. Characteristics of cryptococcal disease among solid-organ transplant recipients in the prior and current cohorts.

Characteristic	Prior cohort (1950–2000)	Current cohort (2001–2008)	*P*
Site of infection			
CNS (*n* = 295)	68	54	.001
Pulmonary			
Pulmonary with other sites (*n* = 48)	29	57	<.001
Only pulmonary (*n* = 84)	14	24	.012
Skin, soft tissue, or osteoarticular (*n* = 42)	12	6	.026
Fungemia (*n* = 38)	22	25	.73
Disseminated disease (*n* = 312)	77	56	<.001
Time to onset after transplantation, median weeks (IQR) (*n* = 219)	88 (26–217)	83 (31–175)	.56
Antifungal agents used for therapy			
All patients			
AmB deoxycholate (*n* = 177)	86	36	<.001
Lipid formulations of AmB (*n* = 64)	4	40	<.001
Fluconazole (*n* = 50)	10	25	<.001
Concurrent use of flucytosine (*n* = 137)	63	38	<.001
With AmB deoxycholate (*n* = 110)	67	71	.64
With lipid formulations of AmB (*n* = 20)	67	28	.049
With fluconazole (*n* = 7)	28	8	.064
Patients with CNS disease			
AmB deoxycholate (*n* = 140)	93	49	<.001
Lipid formulations of AmB (*n* = 47)	3	50	<.001
Fluconazole (*n* = 6)	4	2	.51
Concurrent use of flucytosine (*n* = 115)	70	55	.036
Patients with only pulmonary disease			
AmB deoxycholate (*n* = 18)	70	9	<.001
Lipid formulations of AmB (*n* = 12)	0	26	.012
Fluconazole (*n* = 36)	30	65	.008
Concurrent use of flucytosine (*n* = 10)	24	13	.29

NOTE. Data are percentage of patients, unless otherwise indicated. Amphotericin B, AmB; CNS, central nervous system; IQR, interquartile range; *n,* number of case patients with data available.

$P = .002$). A logistic regression model was constructed to determine the independent role of current era, disseminated disease, type of immunosuppressive regimen, use of lipid formulations of AmB, and renal failure as contributors to overall mortality (table 5). The mortality was lower among patients receiving lipid formulations of AmB, compared with those receiving AmB deoxycholate (odds ratio, 0.16; 95% confidence interval, 0.03–0.84; $P = .03$), and was higher among patients with renal failure at baseline (odds ratio, 5.11; 95% confidence interval, 1.5–17.7; $P = .01$). Current era, disseminated disease, and the type of immunosuppressive regimen were not significantly associated with mortality (table 5).

HSCT recipients. Nine cases of cryptococcosis in HSCT recipients have been reported [75, 89–94]; these included 5 autologous and 2 allogeneic HSCT recipients (table 6). Except for 2 recipients with no data available and 2 who did not receive antifungal prophylaxis at the onset of cryptococcosis, fluconazole was used as prophylaxis for 2 patients, ketoconazole for 1 patient, itraconazole for 1 patient, and caspofungin for 1 patient. One patient had symptoms of cryptococcal meningitis before transplantation, but the diagnosis was established after transplantation. In other patients with data, the time to onset of cryptococcosis was 12 days, 64 days, and 4 months after transplantation. Seven patients had disseminated cryptococcosis (meningitis in 3 patients and cryptococcemia in 4 patients). One patient had cryptococcal pneumonia, and the site of infection was unspecified for another patient. The species of cryptococci were reported for 4 patients, which included *Cryptococcus terreus, Cryptococcus laurentii, Cryptococcus albidus,* and *Cryptococcus adeliensis,* and antifungal regimens are listed in table 6. The sites of isolation of non–*Cryptococcus neoformans* cryptococci were blood in 3 patients and cerebrospinal fluid in 1 patient; the clinical manifestations were reported for 2 patients: one with fever and the other with fever

Table 4. Mortality among solid-organ transplant recipients with cryptococcosis under different clinical conditions.

Variable	Prior cohort (1950–2000)	Current cohort (2001–2008)	*P*
Overall mortality (*n* = 463)	39.9	19.6	<.001
Mortality stratified by			
Site of infection			
Central nervous system (*n* = 270)	51	30	<.001
Pulmonary			
Any sites with pulmonary (*n* = 48)	24	14	.17
Only pulmonary (*n* = 81)	16	7	.22
Skin, soft tissue, or osteoarticular (*n* = 40)	27	25	.93
Disseminated disease (*n* = 286)	50	31	.001
Immunosuppressive regimen			
Tacrolimus based (*n* = 107)	38	9	.002
Cyclosporine A based (*n* = 14)	29	20	.48
Other (*n* = 60)	40	36	.80
Treatment modality			
AmB deoxycholate (*n* = 174)	43	43	.97
Lipid formulations of AmB (*n* = 64)	33	10	.10
Concurrent use of flucytosine (*n* = 137)	42	36	.46
Other variables			
Retransplantation (*n* = 22)	14	13	.95
Rejection (*n* = 51)	33	15	.13

NOTE. Data are percentage of patients, unless otherwise indicated. AmB, amphotericin B; *n*, number of case patients with data available.

and neurological deficits. Outcomes were available for 4 patients: 2 were alive and 2 had died at the end of the follow-up.

Tissue transplant recipients. Five corneal transplant recipients with cryptococcosis were identified in the literature [7–11]; 2 were infected with *C. neoformans,* 2 were infected with *C. albidus,* and 1 was infected with both *C. laurentii* and *Fusarium solani.* Two patients acquired cryptococcal disease through donor-to-host transmission, including 1 donor with disseminated cryptococcosis [7, 8]. One case patient underwent an emergent penetrating keratoplasty for a progressive cryptococcal corneal ulceration, which was diagnosed after transplantation. Cryptococcosis occurred at a median of 2 months after corneal transplantation in 3 patients with data available (for each patient, 2 months, 2 months, and 7 months). The disease was limited to the eye in all 5 patients and constituted cryptococcal keratitis in 4 patients and endophthalmitis in 1 patient.

The first patient underwent keratoplasty for disease progression while receiving treatment with topical miconazole and continued treatment with topical miconazole, prednisolone acetate, and ofloxacin after surgery [10]. She had a best-corrected visual acuity of only hand motions. The second patient received a repeat therapeutic keratoplasty, pars plana vitrectomy, multiple anterior chamber washouts with AmB deoxycholate, intravitreal AmB deoxycholate, and oral fluconazole treatment [11]. Despite these aggressive treatments, enucleation was required. The third patient responded to topical miconazole treatment; no further details were reported about the patient's vision [9]. The fourth patient received topical and systemic AmB deoxycholate and flucytosine treatment and had light perception and residual corneal clouding in the involved eye [7]. Repeat transplantation was performed for the fifth patient, because of the deep location and progression of the corneal lesions. Cryptococcosis was diagnosed after the repeat surgery without treatment of antifungal agents, and her best-corrected visual acuity was 20/40 [8].

DISCUSSION

Evolution of immunosuppressive regimens, prophylactic use of antifungal agents, and advances in surgical techniques have had a substantial impact on the epidemiology and presentation of opportunistic fungal infections in SOT recipients [4, 5, 78, 96, 97]. For example, the incidence of invasive candidiasis and aspergillosis has decreased significantly in SOT recipients within the past decade [3, 5, 98]. However, much less is understood about cryptococcal disease in this regard. Assuming that pub-

Table 5. Logistic regression analysis of variables associated with mortality in solid-organ transplant recipients with cryptococcosis.

Variable	Reference group	OR (95% CI)	*P*
Current era	Prior era	1.08 (0.39–8.36)	.45
Disseminated disease	Localized disease	2.06 (0.35–12.2)	.42
Immunosuppressive regimen			
Tacrolimus based	Non-CNI regimens	0.81 (0.12–8.3)	.83
Cyclosporine A based	Non-CNI regimens	0.34 (0.04–2.5)	.29
Lipid formulations of AmB	AmB deoxycholate	0.16 (0.03–0.84)	.03
Renal failure	No renal failure	5.11 (1.5–17.7)	.01

NOTE. AmB, amphotericin B; CI, confidence interval; CNI, calcineurin inhibitor; OR, odds ratio.

lished reports are representative of emerging trends, our study documents an unchanged incidence of cryptococcosis in SOT recipients.

A number of notable changes have also occurred in the characteristics of the SOT recipients with cryptococcosis in the current era. Patients in the current cohort were older and were more likely to be recipients of multiorgan transplants and of tacrolimus-based treatment regimens. According to the 2007 annual report of the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients, from 1997 to 2006, the percentage of SOT recipients aged >50 years increased from 39.5% to 53.0%, the number of multiorgan transplantations increased from 197 to 566, and use of living donor transplants increased [99]. Additionally, prescription of tacrolimus-based immunosuppressive treatment regimens at 1 year after transplantation increased from the range 12.0%–59.3% in 1996 to the range 60.4%–83.2% in 2005 [99]. These secular trends in transplantation practices and organ-allocation policies likely explain the observed differences in the aforementioned demographic characteristics of the patients with cryptococcosis in the 2 cohorts.

Our study also shows a dramatic shift in the type of cryptococcal disease observed in SOT recipients. Compared with the prior cohort, SOT recipients in the current cohort were less likely to present with CNS or disseminated disease and were more likely to have cryptococcosis limited to the lungs. Although the precise basis for these findings is unclear, it is plausible that changing transplantation practices—including decreased use of OKT3 antibody to treat rejection [99] and wider use of calcineurin inhibitor–based immunosuppressive treatment regimens, particularly regimens that include tacrolimus, which targets the fungal homologues of calcineurin and possesses anticryptococcal activity—accounts for these shifts [100]. Additionally, the use of high-resolution imaging studies in the current era may also contribute to the early diagnosis of pulmonary cryptococcosis.

Antifungal practices for the treatment of cryptococcal disease have also evolved. Polyenes have been regarded as the preferred therapy, particularly for CNS or extrapulmonary cryptococcosis [101]. Our analysis shows that the use of fluconazole and, in particular, lipid formulations of AmB has increased exponentially, whereas use of AmB deoxycholate has decreased correspondingly in the current era. Remarkably, despite evidence documenting a key role for flucytosine in enhancement of fungal clearance [102, 103], its use as induction therapy for SOT recipients with CNS and disseminated disease has decreased significantly. Overall, flucytosine was less likely to be used when induction therapy included lipid formulations of AmB but not AmB deoxycholate and fluconazole. Nevertheless, existing recommendations are to use flucytosine in combination with lipid formulations of AmB as induction treatment for cryptococcal meningoencephalitis [2].

Our study shows that the mortality rate in SOT recipients with cryptococcosis has decreased significantly ($P < .001$) and that this decrease was independent of the effect of calcineurin inhibitor–based treatment regimens, differences in the rate of disseminated disease in the 2 eras, and the study era itself (table 5). As previously reported [1, 78], renal failure remained an independent factor associated with poor outcomes in the present analysis. The use of lipid formulations of AmB was associated with a significant 6-fold decrease in mortality, even when controlled for the aforementioned variables. We caution, however, that our study was not designed to assess the efficacy of antifungal therapy, and other unmeasured confounders could have led to these findings. Limited data currently exist that assess the efficacy of lipid formulations of AmB. In an unpublished, randomized, double-blind trial involving 267 patients with AIDS who had cryptococcal meningitis, mycological success at 2 weeks was 58.3% and 48.0% among patients receiving liposomal AmB at dosages of 3 mg/kg/day and 6 mg/kg/day, respectively, compared with 47.5% among patients receiving AmB deoxycholate at a dosage of 0.7 mg/kg/day [104]. Additionally, liposomal AmB (4 mg/kg/day) demonstrated a higher mycological success rate at 2 weeks than did AmB deoxycholate

Table 6. Hematopoietic stem cell transplant recipients with cryptococcosis.

Year reported [reference]	Transplant source	Age, years; sex	Underlying condition	Conditioning regimen	Time of onset	Infection	Species	Treatment	Outcome
1994 [89]	NA	NA	NA	NA	NA	Cryptococcemia	*Cryptococcus terreus*	NA	NA
1997 [91]	Autologous	17; F	NA	NA	NA	Cryptococcemia	*Cryptococcus laurentii*	Flu	NA
1997 [95]	Allogeneic	12; F	Acute lymphoblastic leukemia	Total body irradiation, thiotepa, cyclophosphamide, and GVHD prophylaxis[a]	64 days	Meningitis	NA	AmBd and 5-FC	Death
2001 [75]	Autologous	NA	NA	NA	NA	Pneumonia	NA	NA	NA
2001 [75]	Autologous	NA	NA	NA	NA	Cryptococcosis	NA	NA	NA
2002 [92]	Autologous	42; F	Multiple myeloma	Melphalan and cyclophosphamide	4 months	Meningitis	NA	LAmB, 5-FC, and Flu	Alive
2004 [93]	Autologous	51; M	T cell lymphoma	Busulfan and etoposide	NA	Cryptococcemia	*Cryptococcus albidus*	AmBd and Flu	Alive
2004 [94]	Allogeneic	40; F	Acute myeloid leukemia	Cyclophosphamide, fludarabine, and antithymocyte globulin	0 days[b]	Meningitis	*Cryptococcus adeliensis*	LAmB and 5-FC	Death
2007 [90]	NA	NA	NA	NA	12 days	Cryptococcemia	*Cryptococcus* species	NA	NA

NOTE. AmBd, amphotericin B deoxycholate; Flu, fluconazole; GVHD, graft-versus-host disease; LAmB, lipid formulations of amphotericin B; NA, not available; 5-FC, 5-flucytosine.

[a] Including cyclosporine, methotrexate, and antilymphocyte globulin.

[b] Symptoms occurred before transplantation; the diagnosis was established after transplantation.

(0.7 mg/kg/day) (66.6% [10 of 15] vs. 11.1% [1 of 9]; $P = .01$), but they showed similar clinical response rates (86% vs. 80%) for human immunodeficiency virus–infected patients with cryptococcal meningitis in another small randomized trial [105].

Cryptococcosis occurs rarely in HSCT recipients. According to the data of US transplant centers (the TRANSNET database), similar numbers of SOTs and HSCTs were performed from 2001 through 2005 (17,226 vs. 16,390), but cryptococcosis developed in 9% of the SOT recipients and 0% of the HSCT recipients [6, 106]. In the world literature, we identified only 9 HSCT recipients with cryptococcosis. Notably, despite the fact that allogeneic transplantation is performed more often than is autologous transplantation (134,746 vs. 122,795 from 1991 through 2007), most cryptococcal cases involved autologous recipients [75, 89–94, 107]. The precise reasons why HSCT recipients are less likely to develop cryptococcosis, compared with SOT recipients, and why autologous HSCT recipients are at greater risk for developing cryptococcal disease, compared with allogeneic HSCT recipients, are not known, although several biological plausibilities exist.

It has been proposed that thymic regeneration in HSCT recipients may render T cells more effective against *Cryptococcus* species [1]. Transplantation of thymic tissue in nude mice was protective against *Cryptococcus* species [108]. Additionally, a T-helper 1 (Th1) cell response characterized by the production of proinflammatory cytokines (e.g., interferon-γ) is protective against cryptococcosis, whereas a T-helper 2 (Th2) cell response with the induction of interleukin 10 is associated with disease progression [109–112]. In HSCT recipients, the conditioning regimen results in damage to the host tissue, especially the intestinal mucosa, and stimulates the secretion of the inflammatory cytokines [113–115]. In allogeneic transplant recipients, these cytokines further activate antigen-presenting cells and, ultimately, donor T cells, leading to the proliferation of Th1 cells [116, 117]. Although induction of Th1 response incurs the risk of acute graft-versus-host disease, which is detrimental to the allogeneic transplant recipients, ironically it may render them less susceptible to *Cryptococcus* infection. In autologous HSCT recipients, on the other hand, the production and messenger RNA expression of Th1 cytokines is severely impaired, whereas the levels of Th2 cytokines is relatively high during first 100 days after transplantation [118, 119]. We speculate that a robust Th1 response may be protective against cryptococcosis in allogeneic HSCT recipients, whereas a dominant Th2 phenotype may account for the susceptibility of autologous HSCT recipients to cryptococcal disease. Because Th2 response predominates in the early posttransplantation period after autologous transplantation and gradually wanes, this scenario also explains why cryptococcosis occurs earlier in autologous HSCT recipients than in SOT recipients (12 days–4 months vs. 18 months after transplantation) [75, 89–94]. Finally, widespread use of fluconazole treatment until engraftment or day 120 may have a protective effect against cryptococcosis in HSCT recipients [120].

A total of 1–2 million tissue and eye transplants, including ~35,000 corneal transplants, are performed annually in the United States [121, 122]. Despite being a rare complication, with only 5 cases identified in the literature, our study underscores the fact that corneal transplants can potentially transmit cryptococcosis [7, 8]. Even though the disease was limited to the eye in all cases, the visual outcomes were uniformly poor.

Several weaknesses of our report should be acknowledged. Foremost among these is that our findings are limited by bias inherent to any retrospective review. Nevertheless, our study summarizes the topical developments and significant trends in characteristics, management practices, and outcomes of this disease among SOT recipients in the current era. Our findings, therefore, may be considered relevant, because they offer comprehensive and updated knowledge of cryptococcosis in these patients. Furthermore, this article is the first to describe unique features of cryptococcal disease in HSCT and tissue transplant recipients.

In summary, the incidence of cryptococcosis in SOT recipients appears to have remained unchanged in the current era. However, further surveillance is warranted, given the escalating use of T cell–depleting antibodies and their potential to increase the risk of fungal infections [66, 123]. SOT recipients with cryptococcosis at present are less likely to have CNS or disseminated disease. Lipid formulations of AmB have emerged as the main treatment option for cryptococcosis and appear to offer a survival benefit for these patients. On the other hand, HSCT recipients present a distinct population of immunocompromised hosts who are much less afflicted by cryptococcosis, compared with SOT recipients. This singular observation deserves further exploration.

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