MAJOR ARTICLE

Unrecognized Pretransplant and Donor-Derived Cryptococcal Disease in Organ Transplant Recipients

Hsin-Yun Sun,[1,22] Barbara D. Alexander,[3] Olivier Lortholary,[23] Francoise Dromer,[24] Graeme N. Forrest,[4,a] G. Marshall Lyon,[5] Jyoti Somani,[5] Krishan L. Gupta,[25] Ramon del Busto,[6] Timothy L. Pruett,[8] Costi D. Sifri,[8] Ajit P. Limaye,[10] George T. John,[26] Goran B. Klintmalm,[11] Kenneth Pursell,[12] Valentina Stosor,[13] Michele I. Morris,[14] Lorraine A. Dowdy,[14] Patricia Munoz,[27] Andre C. Kalil,[16] Julia Garcia-Diaz,[17] Susan L. Orloff,[18] Andrew A. House,[28] Sally H. Houston,[15] Dannah Wray,[19] Shirish Huprikar,[20] Leonard B. Johnson,[7] Atul Humar,[29,a] Raymund R. Razonable,[21] Robert A. Fisher,[9] Shahid Husain,[2,a] Marilyn M. Wagener,[2] Nina Singh,[1,2] and the Cryptococcal Collaborative Transplant Study Group

[1]VA Pittsburgh Healthcare System and [2]University of Pittsburgh, Pittsburgh, Pennsylvania; [3]Duke University Medical Center, Durham, North Carolina; [4]University of Maryland School of Medicine, Baltimore, Maryland; [5]Emory University, Atlanta, Georgia; [6]Henry Ford Hospital, Detroit, [7]St John Medical Center, Detroit, Michigan; Michigan; [8]University of Virginia, Charlottesville, [9]Virginia Commonwealth University, Richmond, Virginia; [10]University of Washington, Seattle; [11]Baylor University Medical Center, Dallas, Texas; [12]University of Chicago and [13]Northwestern University, Chicago, Illinois; [14]University of Miami Miller School of Medicine, Miami, and [15]Tampa General Hospital, Tampa, Florida; [16]University of Nebraska, Omaha, Nebraska; [17]Ochsner Clinic, New Orleans, Louisiana; [18]Oregon Health Sciences University, Portland, Oregon; [19]Medical University of South Carolina, Charleston, South Carolina; [20]Mount Sinai Medical Center, New York, New York; [21]Mayo Clinic, Rochester, Minnesota; [22]Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [23]Institut Pasteur and Faculte de Medecine Paris Descartes, Hopital Necker-Enfants Malades, [24]Institut Pasteur, Paris, France; [25]Postgraduate Institute of Medical Education and Research, Chandigarh, and [26]Christian Medical College Hospital, Vellore, India; [27]Hospital General Universitario Gregorio Maranon and CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain; and [28]University of Western Ontario, London, and [29]University Health Network, Toronto General Hospital, Toronto, Ontario, Canada

Background. Cryptococcosis occurring ⩽30 days after transplantation is an unusual event, and its characteristics are not known.

Methods. Patients included 175 solid-organ transplant (SOT) recipients with cryptococcosis in a multicenter cohort. Very early–onset and late-onset cryptococcosis were defined as disease occurring ⩽30 days or >30 days after transplantation, respectively.

Results. Very early–onset disease developed in 9 (5%) of the 175 patients at a mean of 5.7 days after transplantation. Overall, 55.6% (5 of 9) of the patients with very early–onset disease versus 25.9% (43 of 166) of the patients with late-onset disease were liver transplant recipients ($P = .05$). Very early cases were more likely to present with disease at unusual locations, including transplanted allograft and surgical fossa/site infections (55.6% vs 7.2%; $P < .001$). Two very early cases with onset on day 1 after transplantation (in a liver transplant recipient with *Cryptococcus* isolated from the lung and a heart transplant recipient with fungemia) likely were the result of undetected pretransplant disease. An additional 5 cases involving the allograft or surgical sites were likely the result of donor-acquired infection.

Conclusions. A subset of SOT recipients with cryptococcosis present very early after transplantation with disease that appears to occur preferentially in liver transplant recipients and involves unusual sites, such as the transplanted organ or the surgical site. These patients may have unrecognized pretransplant or donor-derived cryptococcosis.

Cryptococcosis is the third most common invasive mycosis in solid-organ transplant (SOT) recipients, with an overall incidence of ~1.8% (range, 0.3%–5.0%) [1, 2]. The mortality rate among SOT recipients with cryptococcosis, although improved, still approaches 20% [3]. The central nervous system (CNS), lung, and skin or soft tissue are the most common sites of cryptococcal disease [1]. Cryptococcosis typically occurs late after transplantation, with a median time to onset of 16–21 months after transplantation [1, 2]. However, patients with far-advanced end-stage liver disease who developed cryptococcemia within the first week after trans-

Received 22 June 2010; accepted 30 July 2010; electronically published 29 September 2010.

Reprints or correspondence: Dr Nina Singh, Infectious Diseases Section, VA Pittsburgh Healthcare System, University Drive C, Pittsburgh, PA 15240 (nis5@pitt.edu).

Clinical Infectious Diseases 2010; 51(9):1062–1069

1058-4838/2010/5109-0010$15.00
DOI: 10.1086/656584

[a] Present affiliations: University Health Network, Toronto General Hospital, Toronto, Ontario (S. Husain), and University of Alberta, Edmonton, Alberta, Canada. (A. Humar); and Oregon Health Sciences University, Portland, Oregon (G.N.F.).

plantation have been reported [4]. Given the unique susceptibility of cirrhotic patients to cryptococcosis, it is possible that these patients had unrecognized cryptococcal disease before transplantation [5]. Additionally, donor-derived disease has been increasingly recognized as a potential complication of solid-organ transplantation with serious consequences [6–9]. Whether donor-transmitted cryptococcosis plays a role in cryptococcal disease occurring soon after transplantation has not been well defined.

In this context, we observed that, in our cohort of SOT recipients with cryptococcosis, some patients developed disease within 1 month after transplantation, which was far earlier than the expected onset [10]. Clinical characteristics of cryptococcosis that occurs soon after transplantation are not well-delineated in the literature. Thus, we aimed to characterize very early–onset cryptococcal disease in SOT recipients in our cohort and in the literature and to determine whether it is plausible that unrecognized pretransplant or donor-derived cryptococcosis contributes to this rare event.

MATERIALS AND METHODS

SOT recipients with cryptococcosis were enrolled at participating centers during the period 2003–2009. Patient management was in accordance with the standard of care at each center. A detailed description of this cohort has been reported elsewhere [10, 11]. None of the patients were human immunodeficiency virus–positive. Cryptococcosis was defined on the basis of criteria proposed by the European Organization for Research and Treatment in Cancer and the Mycoses Study Group [12]. Data collected included demographic characteristics, type of organ transplant, whether antifungal prophylaxis was received within 6 months before diagnosis, whether an immunosuppressive regimen was being administered at the time of diagnosis, whether renal failure was present at baseline (defined as a serum creatinine level >2 mg/dL at the time of diagnosis), whether the patient had experienced rejection of an earlier transplant (within 6 months of diagnosis), whether the patient was receiving retransplantation, whether the patient had cytomegalovirus infection or disease, the site(s) of cryptococcal disease, the type of antifungal therapy employed, and mortality.

For the purpose of this study, very early–onset and late-onset cryptococcosis were defined as disease occurring ≤30 days and >30 days after transplantation, respectively. Organ sites involved were classified as CNS, pulmonary, skin/soft tissue/osteoarticular; or other sites [1, 10]. Serum or cerebrospinal fluid (CSF) cryptococcal antigen titer ≥1:512 was considered to represent high fungal load, as reported elsewhere [13, 14]. Disseminated infection was defined as CNS infection or fungemia or involvement of ≥2 noncontiguous organ sites [1, 10]. Mortality was assessed at 90 days after diagnosis of cryptococcosis.

Additionally, SOT recipients with cryptococcosis reported in the literature were identified by search of the PubMed database through May 2010 with the terms "cryptococcosis" or "*Cryptococcus*" and "transplantation" or "transplant". Only articles published in English were reviewed. Reference lists of original articles were reviewed for additional cases. Articles were also identified through searches of the authors' own extensive files on these topics [1, 3]. Transplant recipients with disease developing ≤30 days after transplantation were included in the present study.

Statistical analyses. Statistical analyses were performed using Intercooled Stata software, version 9.2 (StataCorp). Categorical data were compared using the χ^2 test or Fisher's exact test. Continuous variables were compared using the rank-sum test.

RESULTS

Of 175 SOT recipients with cryptococcosis, 9 (5%) developed the disease ≤30 days after transplantation. In these 9 patients, cryptococcal disease occurred a mean of 5.7 days after transplantation (interquartile range [IQR], 3–25 days], and 4 of 9 patients developed cryptococcosis within 10 days after transplantation. The demographic and clinical characteristics of patients with very early–onset and late-onset cryptococcosis are presented in Table 1. In all, 55.6% (5 of 9) of the patients with very early–onset disease versus 25.9% (43 of 166) of those with late-onset disease were liver transplant recipients ($P = .05$). On the other hand, patients with very early–onset disease were less likely than those with late-onset disease to be kidney transplant recipients (0 [0%] of 9 vs 79 [47.6%] of 166; $P = .005$). Other characteristics of the patients with very early–onset and late-onset of cryptococcosis are outlined in Table 2. Use of prior antifungal prophylaxis in the study cohort was infrequent (2.2%; 4 of 175 patients). Specifically, none (0 [0%] of 9) of the patients with very early–onset disease and only 2.4% (4 of 166) of the patients with late-onset disease had received prior antifungal prophylaxis ($P = .63$). Fungemia was documented in 44.4% (4 of 9) of the very early–onset and in 25.7% (38 of 148) of the late-onset cases (Table 2). No statistically significant difference between the 2 groups existed with regards to the proportions of patients with disseminated disease, serum or CSF fungal load, and mortality at 90 days (Table 2).

In the 9 patients with very early–onset cryptococcosis, the diagnosis was established by culture in 8 (88.9%) and by histopathological findings in 1 (11.1%). Very early–onset cases were more likely to present with cryptococcal disease at sites (other than pulmonary, CNS, or skin) that included the transplanted allograft and surgical fossa/site infections (5 [55.6%] of 9 vs 10 [6.0%] of 166; $P < .001$) (Table 2). Unrecognized pretransplant cryptococcosis was suspected in patients 1 and 2 (Table 3); these included a liver transplant recipient with *Cryptococcus* isolated from the lung 1 day after transplantation and

Table 1. Comparison of Demographic and Clinical Characteristics between Solid-Organ Transplant Recipients with Very Early Onset Cryptococcosis and Those with Late Onset Cryptococcosis

Variable	Very early onset (≤30 days after transplantation) (n = 9)	Late onset (>30 days) (n = 166)	P
Age, mean years (interquartile range)	56.5 (49–64)	52.7 (45–61)	.337
Male sex	44.4 (4/9)	68.5 (111/162)	.134
Type of transplant			
Liver	55.6 (5)	25.9 (43)	.050
Lung	11.1 (1)	6.6 (11)	
Kidney	0 (0)	47.6 (79)	
Heart	22.2 (2)	10.2 (17)	
Pancreas	0 (0)	2.4 (4)	
Multiorgan	11.1 (1)	1.8 (3)	
Immunosuppression at diagnosis			
Tacrolimus based	66.7 (6)	74.7 (124)	.591
Cyclosporine A based	22.2 (2)	13.9 (23)	.485
Non–calcineurin inhibitor agent based	11.1 (1)	11.4 (19)	.975
T-cell depleting antibodies	11.1 (1)	6.1 (10)	.544
Augmented immunosuppression for prior rejection[a]			
Increase in calcineurin- inhibitor agent	11.1(1)	1.2 (2)	.147
Corticosteroid pulse	11.1(1)	10.2 (17)	.999
T-cell antibodies	0 (0)	1.2 (2)	.999
Renal failure[b]	11.1 (1)	26.5 (44)	.303

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Rejection within 6 months of diagnosis.

[b] Renal failure was defined as serum creatinine >2 mg/dl at the time of diagnosis.

a heart transplant recipient with fungemia and positive serum cryptococcal antigen results on day 1 after transplantation.

An additional 5 of the 9 very early–onset cases (Table 3; patients 3–7) with disease involving the allograft or the surgical sites were likely donor acquired (Table 3). Patient 3 was a single-lung transplant recipient, and the sole site of involvement 3 days after transplantation was the transplanted lung (Table 3). Patient 4 was a liver and kidney transplant recipient, and cultures of his peritoneal and perinephric fluids yielded *Cryptococcus neoformans*. Patient 5 underwent heart transplantation and developed myocarditis and pericarditis after transplantation, with diagnosis established at autopsy. Patients 6 and 7 were both liver transplant recipients with cryptococci in the biliary tract on day 10 and day 21, respectively, one of whom (patient 7) was also fungemic (Table 3). The sources of cryptococcal disease in the remaining 2 of 9 transplant recipients with very early–onset cryptococcosis (ie, a liver transplant recipient with fungemia and CNS and cutaneous disease diagnosed 25 days after transplantation [patient 8] and another liver transplant recipient with pulmonary cryptococcosis that developed 26 days after receipt of the transplant [patient 9]) are less clear (Table 3). Whether these cases represented very early reactivation or whether the patients had pretransplant cryptococcosis could not be determined. Pretransplant serum samples from these patients were not available for testing for cryptococcal antibodies or antigen.

Very early cryptococcosis in SOT recipients in the literature. In the literature, 9 SOT recipients who developed cryptococcosis ≤30 days after transplantation were identified and are summarized in Table 4 [15–23]. Cryptococcosis occurred at a mean of 12.8 days after transplantation (IQR, 7–18 days). Six (66.7%) of the 9 patients were liver transplant recipients, and 4 (57.1%) of the 7 patients with data provided had fungemia. In all, 2 patients received oral nystatin as antifungal prophylaxis at the time of diagnosis, 4 patients did not receive any antifungal prophylaxis, and 3 patients had no data provided. The authors considered unrecognized pretransplant cryptococcosis to be likely in 2 patients, including 1 liver transplant recipient who developed cryptococcal meningitis with cryptococcemia 7 days after transplantation, in whom the pretransplant serum cryptococcal antigen titer was 1:4 [17]. The other case was in a renal transplant recipient with cryptococcal meningitis and cryptococcemia at 14 days after transplantation [15]. Because the disease occurred soon after transplantation, the authors suspected that the patient already had a cryptococcal focus before receiving the transplant.

Donors were proposed to be the source of cryptococcal disease in 2 patients (Table 4). One patient had received a bilateral

Table 2. Comparisons of Characteristics and Outcomes of Cryptococcosis between Solid-Organ Transplant Recipients with Very Early Onset Cryptococcosis and Those with Late Onset Cryptococcosis

Variable	Very early onset (≤30 days after transplantation) (n = 9)	Late onset (>30 days) (n = 166)	P
Site of involvement			
Pulmonary	55.6 (5/9)	55.4 (92/166)	.994
Central nervous system	22.2 (2/9)	53.0 (88/166)	.072
Skin and soft tissue/osteoarticular	11.1 (1/9)	16.9 (28/166)	.651
Other site[a]	55.6 (5/9)	6.0 (10/166)	<.001
Disseminated disease	55.6 (5/9)	60.2 (100/166)	.780
Abnormal mental status	33.3 (3/9)	28.3 (45/159)	.745
Fever	22.2 (2/9)	47.2 (75/159)	.182
Fungemia	44.4 (4/9)	25.7 (38/148)	.217
Cytomegalovirus infection	11 (1/9)	21.5 (35/163)	.687
Serum cryptococcal antigen test			
Positive result	60.0 (3/5)	83.9 (104/124)	.164
Titer ≥1:512	60.0 (3/5)	29.8 (37/124)	.153
Titer, median value (interquartile range)	1:512 (0–1:1024)	1:64 (1:4–1:512)	.859
Cerebrospinal fluid cryptococcal antigen test			
Positive result	75.0 (3/4)	62.3 (81/130)	.605
Titer ≥1:512	25.0 (1/4)	25.4 (33/130)	.986
Titer, median value (interquartile range)	1:2 (1:2–1:256)	1:2 (0–1:512)	.856
Mortality at 90 days	22.2 (2)	15.9 (26)	.620

NOTE. Data are percentage (proportion) of patients unless otherwise indicated. Denominators represent number of patients in whom the variable was reported.

[a] Other sites included peritoneal cavity (1), heart (1), biliary tract (2), and genitourinary tract (1) in the very early group, and genitourinary tract (7), abdominal abscess (1), spinal mass (1), neck mass (1) in the late-onset group; some patients had more than 1 site of involvement.

lung transplant and developed left lobar pneumonia 2 days after transplantation, with fever, leukocytosis, and hypoxemia [18]. *C. neoformans* was isolated from her respiratory tract cultures. Although the authors considered unusually intense environmental exposure as a possible source of infection, they believed that *C. neoformans* could have been transmitted from the allograft [18]. The other case occurred in a renal transplant recipient of an allograft from a 20-year-old donor whose untransplanted kidney showed cryptococcal granulomas on biopsy [21]. Cryptococci were isolated from the urine of the recipient 18 days after transplantation and for a few weeks subsequently [21]. Additionally, 1 liver transplant recipient developed disseminated cryptococcosis with involvement of the liver, lung, CNS, and fungemia 10 days after transplantation [19]. The biopsy of the transplanted liver was reported to be negative for *C. neoformans*.

DISCUSSION

Most post-transplantation cryptococcosis is considered to represent reactivation of latent or quiescent infection in the recipient [24]. Assessment of pretransplant serum samples for cryptococcal-specific antibodies documented that a majority of the SOT recipients with cryptococcosis exhibited serological evidence of infection before transplantation [25]. Although these patients developed cryptococcal disease significantly earlier after transplantation than did those without serological evidence of infection, the median time to onset of disease in patients with prior antibody reactivity and presumed reactivation disease was still 5.6 months [25]. Development of cryptococcosis within 1 month after transplantation is therefore unusual. Our study shows that this entity occurs in 5% of transplant recipients with cryptococcosis and has unique characteristics and disease manifestations.

Generally, the degree of immunosuppression is higher in the early post-transplantation period, although no significant differences in disease severity in terms of fungal load and mortality at 90 days were observed between very early–onset and late-onset disease (Table 2). However, very early–onset cryptococcosis appears to occur preferentially in liver transplant recipients. Indeed, 55.6% and 66.7% of our patients with very early–onset cryptococcosis and patients with very early–onset cryptococcosis reported in the literature, respectively, were liver

Table 3. Characteristics of Donors and Solid-Organ Transplant Recipients with Cryptococcosis that Developed ⩽30 Days after Transplantation

Patient	Type	Recipient age and sex	Recipient characteristics	Time to onset, days	Sites of disease	Serum cryptococcal titer	Fungemia	Outcome at 90 days of treatment	Proposed source
1	Liver	65/F	Hepatitis C virus infection	1	Lung	Negative	No	Alive	Recipient
2	Heart	49/M	Ischemic heart disease	1	Blood	1:8	Yes	Alive	Recipient
3	Lung	64/M	COPD	3	Lung	NA	No	Alive	Donor
4	Liver/kidney	59/M	Cryptogenic cirrhosis, end-stage renal disease	25	CNS, lung, abdominal cavity,[a] blood	1:512	Yes	Death	Donor
5	Heart	57/F	Ischemic cardiomyopathy	30	Heart,[b] lung	NA	No	Death	Donor
6	Liver	49/M	Primary biliary cirrhosis	10	Biliary tract[c]	NA	No	Alive	Donor
7	Liver	61/M	Hepatitis C virus infection	21	Biliary tract, GU,[d] blood	>1:1024	Yes	Alive	Donor
8	Liver	64/M	Hepatitis C virus infection	25	CNS, groin,[e] skin, blood	1:1024	Yes	Alive	Unknown
9	Liver	43/F	Hepatitis C virus infection	26	Lung	Negative	No	Alive	Unknown

NOTE. CNS, central nervous system; COPD, chronic obstructive pulmonary disease; NA, not available.

[a] Culture of peritoneal and perinephrenic fluid positive for *Cryptococcus neoformans*.
[b] Myocarditis and pericarditis.
[c] Bile culture positive for *C. neoformans*.
[d] Urine culture positive for *C. neoformans*.
[e] A mass over groin area and culture positive for *C. neoformans*.

Table 4. Characteristics of Donors and Solid-Organ Transplant Recipients with Cryptococcosis that Developed ⩽30 Days after Receipt of Transplant

Study	Type	Recipient age and sex	Recipient characteristics	Time to onset, days	Site(s) of disease	Serum cryptococcal titer	Fungemia	Outcome	Proposed source
Fishman et al [17]	Liver	45/M	HCV, preTx cryptococcal titer 1:4	7	Blood, CNS	1:128	Yes	Death	Recipient
Nicol et al [15]	Renal	34/M	Chronic glomerulonephritis	14	Blood, CNS	1:8000	Yes	Alive	Recipient
Kanj et al [18]	Lung	24/F	Pulmonary hypertension (native lung biopsy: focal lymphoid infiltrate with recent hemorrhage)	2	Lung	Negative	No	Alive	Donor
Ooi et al [21]	Renal	29/F	End-stage renal disease	18	Kidney	NA	No	Alive	Donor
Lu et al [19]	Liver	54/M	HCV	10	Blood, CNS, liver, lung	>1:2048	Yes	Death	NA
Alexander et al [16]	Liver	NA	NA	25	Blood, CNS	NA	Yes	NA	NA
Moe et al [20]	Liver	35/M	End-stage liver disease	21	Skin	Positive	No	Death	NA
Silveira et al [22]	Liver	NA	NA	7	Lung	Negative	NA	Alive	NA
Xia et al [23]	Liver	63/M	NA	11	Lung	NA	NA	Death	NA

NOTE. CNS, central nervous system; HCV, hepatitis C virus infection; NA, not available; preTX, pretransplant.

transplant recipients (Tables 3 and 4). This finding may be related to the susceptibility of liver transplant recipients during transplant candidacy to cryptococcosis. A growing body of evidence suggests that cirrhosis-associated compromised host defenses (such as impaired cell mediated immunity, phagocytic dysfunction, decreased antibody and immunoglobulins, and complement deficiency) is a significant risk factor for cryptococcosis [5]. Furthermore, fungemia occurs in a significant proportion (67%) of patients with cirrhosis-related cryptococcosis [5], a feature that was also observed in SOT recipients with very early–onset cryptococcosis, both in our cohort and in the literature; 44.4% and 57.1%, respectively, had fungemia (Tables 1, 2, and 4).

Several lines of evidence suggest that, in some cases, very early–onset cryptococcal disease may represent unrecognized pretransplant cryptococcosis. These include documentation of pulmonary disease, fungemia, or cryptococcal antigen positivity as early as day 1 after transplantation in 2 of our patients. Additionally, donor-derived cryptococcosis occurs [18, 21, 26]. CNS, lung, and skin are the most common sites of cryptococcosis in SOT recipients [1]. Indeed 3 of 6 liver transplant recipients in our study had lung disease. However, unusual sites of presentation, such as the transplanted organ as the sole or major site of involvement or isolation of this yeast from surgical sites (abdominal cavity, renal fossa, and biliary tract), suggest that the disease may have been transmitted from the donor. It is also plausible that some cases of cryptococcosis that occur within the first month after transplantation represent early reactivation, particularly after liver transplantation. A state of iron overload in liver transplant recipients that impairs cryptococcal host defenses has been proposed to increase the risk of disseminated disease and may also predispose these patients to early disease after transplantation [27, 28].

Our study has relevant implications for care providers. Foremost among these is the awareness that cryptococcosis can exist in the recipients before transplantation, even in the absence of iatrogenic immunosuppression, such as the use of corticosteroids. For example, 67% of the patients with end-stage liver disease and cryptococcosis in 1 study had no other underlying predisposing condition [5]. Untreated cryptococcal disease would preclude transplantation; however, indolent pretransplant disease may be unveiled by immunosuppressive therapy with overt disease presenting only after transplantation. Fungemia was documented in 44.4% of our patients with very early disease. Thus, although candidemia occurs more commonly than cryptococcemia in the early post-transplantation period, "yeast isolates" in the blood cultures should be fully identified, given that use of echinocandins is becoming an increasingly common practice for the treatment of fungemia, and these agents have no activity against cryptococci. Finally, surgical site cultures that yield cryptococci should warrant consideration of donor-derived disease. Various types of organ (Tables 3 and 4) and tissue allografts, such as cornea [3], potentially have the ability to transmit cryptococcosis, and because retrieved organs from a single donor may be used for multiple recipients, prompt notification of organ procurement agencies when donor-derived disease is suspected is crucial.

Several weaknesses of our study deserve to be acknowledged. Because the study was not specifically designed to assess allograft-transmitted disease, detailed information regarding donors was lacking, and retrieval of donor isolates for strain typing was not feasible. However, even in clinical practice, acquisition of donors' medical history is challenging, particularly when they have unexpected or unidentified diseases. Furthermore, depending upon the extent to which the information is accessible, the quality of these data can vary considerably. In addition, pretransplant information for recipients was not available in our cohort to support or refute the argument that, in some cases, cryptococcal disease existed prior to transplantation. Regardless, their pretransplant condition did not offer sufficient clues to physicians to consider the possibility of cryptococcosis and defer transplantation.

In summary, very early–onset post-transplantation cryptococcosis occurs most frequently among liver transplant recipients, often presents with cryptococcemia, and is characterized by involvement of unusual sites, such as the transplanted organ or surgical sites. Some of these patients may have unrecognized pretransplant or donor-derived disease.

Acknowledgments

Potential conflicts of interest. B.D.A. has served on advisory boards for Abbott, Bristol Myers Squibb, bioMérieux, and has received investigator-initiated grants from Astellas and Pfizer. O.L. has served on speaker's bureaus of Astellas, Gilead Sciences, Merck, Schering-Plough, and Pfizer and as a consultant for Astellas and Gilead Sciences. G.F. has received grant support from Astellas. G.M.L. has served on advisory boards for and received grants from Merck and Astellas and on speaker's bureaus of Astellas, Schering-Plough, and Wyeth. A.P.L. has served on consultant boards for Pfizer and Merck and has contracted research for Pfizer. M.I.M. has served on advisory boards for Astellas, Pfizer, and Merck; has received grants from Astellas, Basilea, and Pfizer; and has served on speaker's bureaus of Astellas and Pfizer. P.M. has served on speaker's bureaus of Merck and Novartis and on an advisory board for Pfizer. S.H.H. has served on speaker's bureaus of Astellas and Pfizer. L.B.J. has served on a speaker's bureau of Pfizer. S.H. has received grants from Pfizer, Astellas, and Merck. N.S. has received investigator-initiated grant support from Pfizer. All other authors: no conflicts.

Financial support. National Institutes of Health, National Institute of Allergy and Infectious Diseases (R01 AI 054719–01 to N.S.)

References

1. Husain S, Wagener MM, Singh N. *Cryptococcus neoformans* infection in organ transplant recipients: variables influencing clinical characteristics and outcome. Emerg Infect Dis **2001**; 7:375–381.
2. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis **2010**; 50:1101–1111.

3. Sun HY, Wagener MM, Singh N. Cryptococcosis in solid-organ, hematopoietic stem cell, and tissue transplant recipients: evidence-based evolving trends. Clin Infect Dis **2009**; 48:1566–1576.
4. Winston DJ, Emmanouilides C, Busuttil RW. Infections in liver transplant recipients. Clin Infect Dis **1995**; 21:1077–1089; quiz 90–91.
5. Singh N, Husain S, De Vera M, Gayowski T, Cacciarelli TV. *Cryptococcus neoformans* infection in patients with cirrhosis, including liver transplant candidates. Medicine (Baltimore) **2004**; 83:188–192.
6. Transplantation-transmitted tuberculosis—Oklahoma and Texas, 2007. MMWR Morb Mortal Wkly Rep **2008**; 57:333–336.
7. Palacios G, Druce J, Du L, et al. A new arenavirus in a cluster of fatal transplant-associated diseases. N Engl J Med **2008**; 358:991–998.
8. Srinivasan A, Burton EC, Kuehnert MJ, et al. Transmission of rabies virus from an organ donor to four transplant recipients. N Engl J Med **2005**; 352:1103–1111.
9. Iwamoto M, Jernigan DB, Guasch A, et al. Transmission of West Nile virus from an organ donor to four transplant recipients. N Engl J Med **2003**; 348:2196–2203.
10. Singh N, Alexander BD, Lortholary O, et al. *Cryptococcus neoformans* in organ transplant recipients: impact of calcineurin-inhibitor agents on mortality. J Infect Dis **2007**; 195:756–764.
11. Sun HY, Alexander BD, Lortholary O, et al. Lipid formulations of amphotericin B significantly improve outcome in solid organ transplant recipients with central nervous system cryptococcosis. Clin Infect Dis **2009**; 49:1721–1728.
12. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis **2002**; 34:7–14.
13. Dromer F, Mathoulin-Pelissier S, Launay O, Lortholary O. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. PLoS Med **2007**; 4:e21.
14. Lortholary O, Poizat G, Zeller V, et al. Long-term outcome of AIDS-associated cryptococcosis in the era of combination antiretroviral therapy. AIDS **2006**; 20:2183–2191.
15. Nicol AJ, Cassidy MJ, Michalowsky K, Kahn D. Use of intralipid as a vehicle for amphotericin B in the treatment of cryptococcal meningitis in a renal transplant recipient. Nephron **1996**; 73:312–313.
16. Alexander J, Limaye AP, Ko CW, Bronner MP, Kowdley KV. Association of hepatic iron overload with invasive fungal infection in liver transplant recipients. Liver Transpl **2006**; 12:1799–1804.
17. Fishman JA, Gonzalez RG, Branda JA. Case records of the Massachusetts General Hospital. Case 11–2008. A 45-year-old man with changes in mental status after liver transplantation. N Engl J Med **2008**; 358: 1604–1613.
18. Kanj SS, Welty-Wolf K, Madden J, et al. Fungal infections in lung and heart-lung transplant recipients: report of 9 cases and review of the literature. Medicine (Baltimore) **1996**; 75:142–156.
19. Lu S, Furth EE, Blumberg EA, Bing Z. Hepatic involvement in a liver transplant recipient with disseminated cryptococcosis. Transpl Infect Dis **2009**; 11:179–82.
20. Moe K, Lotsikas-Baggili AJ, Kupiec-Banasikowska A, Kauffman CL. The cutaneous predilection of disseminated cryptococcal infection in organ transplant recipients. Arch Dermatol **2005**; 141:913–914.
21. Ooi BS, Chen BT, Lim CH, Khoo OT, Chan DT. Survival of a patient transplanted with a kidney infected with *Cryptococcus neoformans*. Transplantation **1971**; 11:428–429.
22. Silveira FP, Husain S, Kwak EJ, et al. Cryptococcosis in liver and kidney transplant recipients receiving anti-thymocyte globulin or alemtuzumab. Transpl Infect Dis **2007**; 9:22–27.
23. Xia D, Yan LN, Xu L, et al. Postoperative severe pneumonia in adult liver transplant recipients. Transplant Proc **2006**; 38:2974–2978.
24. Singh N, Dromer F, Perfect JR, Lortholary O. Cryptococcosis in solid organ transplant recipients: current state of the science. Clin Infect Dis **2008**; 47:1321–1327.
25. Saha DC, Goldman DL, Shao X, et al. Serologic evidence for reactivation of cryptococcosis in solid-organ transplant recipients. Clin Vaccine Immunol **2007**; 14:1550–1554.
26. Ison MG, Hager J, Blumberg E, et al. Donor-derived disease transmission events in the United States: data reviewed by the OPTN/UNOS Disease Transmission Advisory Committee. Am J Transplant **2009**; 9: 1929–1935.
27. Singh N, Sun HY. Iron overload and unique susceptibility of liver transplant recipients to disseminated disease due to opportunistic pathogens. Liver Transpl **2008**; 14:1249–1255.
28. Singh N, Aguado JM, Bonatti H, et al. Zygomycosis in solid organ transplant recipients: a prospective, matched case-control study to assess risks for disease and outcome. J Infect Dis **2009**; 200:1002–1011.