Disseminated Cryptococcosis After Liver Transplant: A Case Report

Gabriel Sebastián Díaz-Ramírez,[1] Omar Yesid Martínez-Casas,[1] Juan Ignacio Marín-Zuluaga,[2,3] Octavio Muñoz-Maya,[2,3] Óscar Santos-Sánchez,[2,3] Isabel Cristina Ramírez,[4] Juan Carlos Restrepo-Gutiérrez[2,3]

Abstract

Cryptococcosis is an opportunistic infection caused by the Basidiomycota *Cryptococcus neoformans* (*Cryptococcus gattii*), which affects immunosuppressed patients and less frequently immunocompetent patients. Solid-organ transplant recipients are a particularly high-risk group, depending on the net state of immunosuppression. In these patients, the infection usually appears after the first year after transplant, although it may occur earlier in liver transplant recipients. In most cases, the infection is secondary to the reactivation of a latent infection, although it may be due to an unidentified pretransplant infection by primary infection. Less frequently, it may be transmitted by the graft. The lung and central nervous system are most frequently involved. Extrapulmonary involvement is seen in 75% of the cases, and disseminated disease occurs in 61%, with mortality ranging from 17% to 50% when the central nervous system is involved. Here, we report a case of disseminated cryptococcosis (lymphadenitis, meningitis, pulmonary nodules, and possibly sacroiliitis) in a patient after liver transplant, with good clinical and microbiological outcomes and without relapse.

Key words: Cryptococcus neoformans, *Joint pain, Liver cirrhosis*

Introduction

Cryptococcosis is an opportunistic fungal infection that affects immunosuppressed and less frequently immunocompetent patients. Most cases are caused by *Cryptococcus neoformans (Cryptococcus gattii)*, and the primary route of infection is by inhalation.[1] In patients without human immunodeficiency virus, the infection is generally associated with immuno-suppression secondary to solid-organ transplant (SOT) and transplant of hematopoietic progenitors in those who receive immunosuppressive agents and in those who present with sarcoidosis, primary immunodeficiency, autoimmune, or liver diseases.[2]

Patients who are SOT recipients are at risk of cryptococcosis, with an incidence that reaches 5.3%.[3] It is usually a late-onset infection (after the first year posttransplant)[4,5] but may have an early onset, particularly in patients undergoing liver or lung transplant compared with renal transplant recipients. This may be explained by the intensity of immuno-suppressive treatment.[6] In most cases, infection occurs because of reactivation of a latent infection, although it can occur after transplant following a primary infection. In rare cases, it can be transmitted by the graft.[7]

The lung and central nervous system (CNS) are most frequently involved in the infection; however, in up to 61% of liver transplant patients, it manifests as disseminated disease, with extrapulmonary involvement in 75% of the cases.[6] Other less frequently affected sites include the skin (nodules, papules, ulcers, abscesses, cellulitis, and panniculitis),[8] soft tissues, and osteoarticular system in 6% to 12% of patients.[3] The liver, kidneys, and prostate are less frequently involved. The mortality rate in disseminated disease is 17% and is close to 50% when the CNS is involved.[6]

We report a case of disseminated cryptococcosis (lymphadenitis, meningitis, pulmonary nodules, and possibly, sacroiliitis) presenting early in a patient after liver transplant, with good clinical and microbiological outcomes and without relapse.

Case Report

A 44-year-old Colombian woman presented with portal hypertension and cirrhosis secondary to autoimmune hepatitis complications, grade 3 esophageal varices without bleeding, and refractory ascites without spontaneous peritonitis (Child-Pugh class C score of 12 and Model for End-Stage Liver Disease score of 25). She did not receive immunosuppressive drugs for autoimmune hepatitis treatment, and she had no exposure to bird or bat guano. In January 2017, she underwent orthotopic liver transplant. In the perioperative period, she received antibacterial prophylaxis with piperacillin-tazobactam for 48 hours and anidulafungin for 10 days, according to institutional protocol. The antifungal agent was used because of the high risk of mold infection (elevated transfusion support and acute kidney injury per the Kidney Disease: Improving Global Outcomes score of 3, with dialysis therapy until day 7). She did not receive immunosuppression-inducing agents and achieved full recovery of renal function. She was in cytomegalovirus (CMV) preemptive strategy because her CMV risk was intermediate (immunoglobulin G donor positive/immunoglobulin G recipient positive); all viral loads were negative. She was discharged from the hospital on posttransplant day 10. The patient was started on immunosuppressive treatment (prednisolone at 20 mg/day, conventional tacrolimus at 5 mg every 12 h, and mycophenolate mofetil at 1000 mg every 12 h) and prophylaxis with trimethoprim-sulfamethoxazole, nystatin, and

acyclovir (the latter during the first month posttransplant).

On posttransplant day 49, she was readmitted for 2 weeks due to headache associated with bilateral sacroiliac joint pain. On physical examination, the patient was found to be afebrile, awake, and without meningeal signs; however, pain and limitation were found when moving the bilateral sacroiliac articulation. Laboratory tests showed leukocytosis with deviation to the left, elevation of C-reactive protein, and good renal and hepatic graft function (Table 1). Magnetic resonance imaging showed bilateral chronic inflammation in the sacroiliac joints and multiple intraperitoneal and retroperitoneal enlarged lymph nodes. Neck and chest tomography showed multiple supraclavicular and infraclavicular lymphadenopathies and a pulmonary nodule in the medial segment of the middle lobe (Figure 1), with normal brain magnetic resonance imaging.

An exploratory laparotomy was performed, with resection of retroperitoneal nodes, and a percutaneous lung biopsy, guided by tomography, as well as lumbar puncture, with normal cerebrospinal fluid (CSF) opening pressure, were performed. A posttransplant lymphoproliferative disorder was ruled out. Lateral flow assay revealed *Cryptococcus* antigen in the blood, which tested positive at a dilution of 1/2560.

Cerebrospinal fluid studies showed lymphocytic pleocytosis and hypoglycorrhachia and tested positive for *Cryptococcus* antigen. Chromogenic agar and Sabouraud agar cultures of the sample obtained from the retroperitoneal adenopathy and CSF
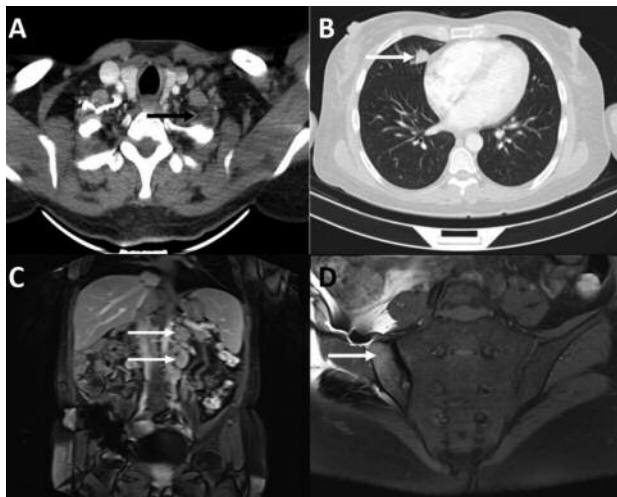
Table 1. Laboratory Data on Admission

Parameter	Result	Reference Value	Parameter	Result
Hemoglobin, g/dL	10	13-17	Serum *C. neoformans* antigen (LFA)	1:2560
White blood cells, per mm³	20400	4500-11000	CSF *C. neoformans* antigen (LFA)	1:40
Neutrophils, %	75	50-70	CSF analysis	
Lymphocytes, %	14.0	20-45	Protein	40
Platelets, per mm³	289000	150000-450000	Glucose	54
C-reactive protein, mg/dL	28	0.01-0.82	Leukocytes	160
Creatinine, mg/dL	0.72	0.6-1.1	Lymphocytes	99,0
Blood urea nitrogen, mg/dL	14	8-25	VDRL	Negative
AST, U/L	13	5-34	HIV antibodies	Negative
ALT, U/L	16	0-55	CMV viral load	Negative
ALP, U/L	108	40-150	EBV viral load	Negative
GGT, U/L	57	12-64	Aerobic blood cultures	Negative
Total bilirubin, mg/dL	1.1	0.2-1.2	Fungal blood cultures	Negative
Direct bilirubin, mg/dL	0.5	0.1-0.5	GeneXpert (lung tissue)	Negative
Lactic dehydrogenase, U/L	127	125-243	Mycobacterial culture (lung tissue)	Negative
Tacrolimus, ng/mL	9.4	5-10		

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; GGT, gamma-glutamyltransferase; HIV, human immunodeficiency virus; LFA, lateral flow assay; VDRL, Venereal Disease Research Laboratory test

showed *C. neoformans* growth (Figure 2), with susceptibility to fluconazole (minimum inhibitory concentration < 2 µg/mL) and amphotericin B (minimum inhibitory concentration < 0.5 µg/mL). The histology of the retroperitoneal adenopathy and pulmonary nodule showed chronic granulomatous inflammation without caseous necrosis, and methenamine silver and mucicarmine stains were positive

for blastoconidia compatible with *Cryptococcus* (Figure 3). A pan-fungal polymerase chain reaction assay was positive for *C. neoformans.* Diagnostic testing using GeneXpert (Cepheid, Medellin, Columbia) was negative for mycobacteria, and blood cultures for aerobes and fungi were also negative (Table 1).

Disseminated cryptococcosis without crypto-coccemia was confirmed with meningeal, pulmonary, and lymph node involvement. Antifungal induction therapy was initiated with amphotericin B (0.7 mg/kg/day) and flucytosine (100 mg/kg/day). In addition, the dose of immunosuppressant therapy was reduced to 4 mg tacrolimus every 12 hours, 10 mg/day prednisolone, and 500 mg mycophe-

**Figure 1.** Neck and Chest Tomography

(A) Enlarged cervical lymph nodes. **(B)** Pulmonary nodule (1.5 cm) shown with contrast abdominal magnetic resonance imaging. **(C)** Enlarged retroperitoneal lymph nodes. **(D)** Axial fat-suppressed T2-weighted, high signal area in the iliac bone and surrounding muscle, with bone marrow edema in the left iliac bone (arrow).

Figure 2. Chromogenic Agar and Sabouraud Agar Cultures of Sample Obtained From the Retroperitoneal Adenopathy and Cerebrospinal Fluid Showing *Cryptococcus neoforman*s Growth
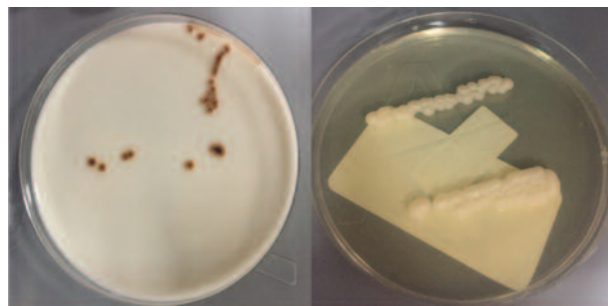
(Left) Sabouraud dextrose agar at 30°C. **(Right)** After 5 days of incubation of lymph node specimen.

Figure 3. Histology of the Retroperitoneal Adenopathy and Pulmonary Nodule (×40)
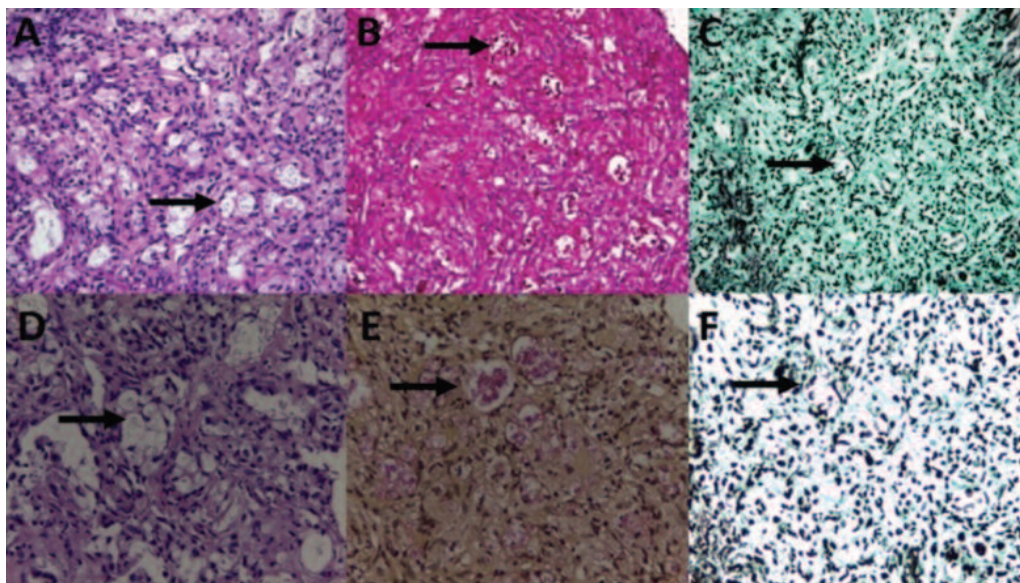
(A) Hematoxylin-eosin stain showing chronic granulomatous inflammation without caseous necrosis. Mucicarmine stain **(B)** and methenamine silver stain **(C)** showing yeast forms compatible with *Cryptococcus* species. **(D)** Hematoxylin-eosin stain showing chronic granulomatous inflammation of pulmonary nodule. **(E)** Mucicarmine stain showing encapsulated yeast forms. **(F)** Methenamine silver stain showing yeast forms compatible with *Cryptococcus* species.

nolate mofetil every 8 hours. On day 4 of treatment, a sacroiliac joint biopsy was performed. Fungal cultures were negative, and histology showed chronic inflammation and fibrosis, with negative methenamine silver and mucicarmine stains. The induction antifungal treatment was extended to 3 weeks, with resolution of symptoms, CSF culture sterilization, and normalization of CSF parameters. Hospital discharge included consolidation treatment with fluconazole at 400 mg/day. At 10 months posttransplant, the patient remains asymptomatic, without relapse and with good graft function.

Discussion

Liver transplant is a treatment option for patients with acute and chronic liver diseases,[9] with good short- and long-term results due to patient selection, improved surgical techniques and perioperative care, and development of more effective immunosuppressive drugs.[10] However, opportunistic infections frequently occur in such patients and are one of the main causes of death.[9]

Up to 8% of fungal diseases after SOT are caused by *Cryptococcus* species; these are the third most common type of fungal infection after *Candida* and *Aspergillus* species.[11] The incidence of *Cryptococcus* species in liver transplant is as high as 5.3%.[3] Our reported patient had risk factors for infection caused by *Cryptococcus* due to advanced autoimmune liver disease, renal failure requiring renal replacement therapy in the early posttransplant period, and use of immunosuppressants, particularly corticosteroids. All of these risk factors affect the net state of immunosuppression, which is also determined by the cause of the disease for which the transplant was indicated, the type and duration of immunosuppressive treatment, the integrity of the mucocutaneous barriers, the presence of metabolic conditions (diabetes, malnutrition, and uremia), and coinfection with immunomodulatory viruses such as CMV, Epstein-Barr virus, and human immunodeficiency virus, among others.[4] Furthermore, it is important to note that our patient received antifungal prophylaxis with anidulafungin, although this agent is not active against *Cryptococcus*.

Most cases of cryptococcal infection in SOT recipients occur after the first year posttransplant,[4,5] with a median occurrence at 20 months.[11] In most cases, this is due to a reactivation of a latent infection.[7] In our patient, the disease was of early onset (second month), which is more common in liver transplant than in kidney transplant recipients.[6] In early-onset infection, particularly when it occurs in the first 30 days posttransplant, the possibility of an unidentified pretransplant infection[12] and transmission from the graft[13] should be considered. However, our patient did not have the most common clinical presentations shown in these cases, such as graft involvement and surgical wound or unusual sites of infection. No information was available about whether the other recipient of kidneys from the same donor had cryptococcal infection.

In the case presented here, disseminated involvement (meningeal, pulmonary, and lymph node) by *C. neoformans* was documented, which is described in literature as occurring in up to 61% of patients[6] because the CNS and lung are the most frequently compromised sites.[7] Despite the clinical signs, images, and biopsy compatible with sacroiliitis, no *Cryptococcus* was demonstrated in the joint. This is possibly because the surgical sample was obtained after 4 days of exposure to effective antifungal therapy. After treatment, complete resolution of the joint symptoms was also achieved, indicating a possible joint infection, which has infrequently been described.[1]

Finally, the mortality rate in disseminated cryptococcosis is around 17% and increases to almost 50% when the CNS is involved, particularly in the presence of factors predictive of 90-day mortality, such as cryptococcemia, compromised in the state of consciousness, and intracranial hypertension (CSF opening pressure ≥ 25 cmH$_2$O).[1] Our patient did not have any of the factors described above, and her response to treatment was favorable and without complications.

In conclusion, cryptococcosis is an opportunistic infection that may occur early after SOT; this is often accompanied by pulmonary, systemic, and/or CNS infection. Other sites are also less frequently involved but with high morbidity, according to the associated risk factors.

References

1. Pappas PG. Cryptococcal infections in non-HIV-infected patients. *Trans Am Clin Climatol Assoc*. 2013;124:61-79.
2. Williamson PR, Jarvis JN, Panackal AA, et al. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. *Nat Rev Neurol*. 2017;13(1):13–24.

3. Sun H, Wagener MM, Singh N. Cryptococcosis in solid-organ, hematopoietic stem cell, and tissue transplant recipients: Evidence-based evolving trends. *Clin Infect Dis.* 2009;48(11):1566–1576.

4. Fishman JA, Rubin RH. Infection in organ transplant recipients. *N Engl J Med.* 1998;338(24):1741-1751.

5. Husain S, Wagener MM, Singh N. Cryptococcus neoformans infection in organ transplant recipients: variables influencing clinical characteristics and outcome. *Emerg Infect Dis.* 2001; 7(3):375-381.

6. 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(5):756–64.

7. Baddley JW, Forrest GN. Cryptococcosis in solid organ transplantation. *Am J Transplant.* 2013;13(Suppl.4):242-249.

8. Sun HY, Alexander BD, Lortholary O, et al. Cutaneous cryptococcosis in solid organ transplant recipients. *Med Mycol.* 2010;48(6):785-791.

9. Burra P, Burroughs A, Graziadei I, et al. EASL clinical practice guidelines: Liver transplantation. *J Hepatol.* 2016;64(2):433-485.

10. Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. *Am J Transplant.* 2010;10:1003-1019.

11. 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(8):1101-1111.

12. Sun H, Alexander BD, Lortholary O, et al. Unrecognized pretransplant and donor-derived cryptococcal disease in organ transplant recipients. *Clin Infect Dis.* 2010;51(9):1062-1069.

13. Baddley JW, Schain DC, Gupte AA, et al. Transmission of Cryptococcus neoformans by organ transplantation. *Clin Infect Dis.* 2011;52(4):e94-e98.