Cluster of Donor-Derived Cryptococcosis after Liver and Kidney Transplantation

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Cryptococcosis is the third most common invasive fungal infection in solid-organ transplants (1,2). The incidence of cryptococcosis in transplant recipients was estimated to be 0.76% in mainland China, and the Cryptococcus neoformans variant grubii genotype was the predominant species (3–5).

Cryptococcosis after transplantation is easily overlooked because of high diversity of clinical symptoms, which leads to mortality rates as high as 20% (6). Another feature of recipient-acquired cryptococcosis is the late onset of infection, which usually is 15–21 months posttransplant (7). However, donor-derived transmission should be considered if disease is found within 1 month posttransplant or if multiple recipients from the same donor become ill (8,9). We report a cluster of donor-derived cryptococcosis after liver and kidney transplantation in China.

This study was approved by the Administration Committee of Shanghai Jiao Tong University, China. Written informed consent was obtained from the patient for the anonymized information to be published in this article.

The transplant donor was a 60-year-old man who had hepatocellular carcinoma and underwent liver transplantation. The transplant was successful, and there were no immediate complications. Postoperative aminotransferase levels decreased gradually. However, the recipient had progressive jaundice. The total bilirubin level increased from 103.6 µmol/L on postoperative day (POD) 1 to 704.3 µmol/L on POD 15. The patient had no fevers, cough, or dizziness.

Liver biopsy on POD 7 showed no evidence of rejection, biliary complications or drug-induced liver injury. The unexpected jaundice persisted and showed no major decrease. Liver biopsy was performed on POD 30. Large numbers of encapsulated yeasts were found inside the liver. Microscopically, the colonized organism had an oval shape and a loose surrounding histiocytic response (Figure). A subsequent recipient serum sample was positive for CrAg (titer >1:2,560) on POD 32.

The recipient received amphotericin B lipid complex plus 5-flucytosine for 4 weeks. A gradual decrease in bilirubin was observed. The antifungal treatment was changed to oral fluconazole after he was discharged. Follow-up of CrAg showed a decrease from 1:2,560 to 1:32 at 1 year after transplant. Fluconazole was discontinued 15 months after transplant. The recipient showed good liver function for 30 months without active infection (Table). Hepatocellular carcinoma did not recur.

The second recipient was a 65-year-old man who had end-stage renal disease and received a kidney transplant from the same donor. The graft function recovered uneventfully. The recipient was discharged on POD 6 and received an immunosuppression regimen of tacrolimus and mycophenolate. However, the recipient had a low fever and cough on POD 21. Chest CT showed pulmonary consolidations and infiltration. Bronchoalveolar lavage was not performed because intubation was not conducted; there were no signs of hypoxia. However, a CrAg titer of 1:1,280 and positive blood culture 2 blood cultures at the time of organ procurement became positive after 8 days of incubation. C. neoformans was subsequently identified.

The first recipient was a 64-year-old man who had hepatocellular carcinoma and underwent liver transplantation. The transplant was successful, and there were no immediate complications. Postoperative aminotransferase levels decreased gradually. However, the recipient had progressive jaundice. The total bilirubin level increased from 103.6 µmol/L on postoperative day (POD) 1 to 704.3 µmol/L on POD 15. The patient had no fevers, cough, or dizziness.

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The third recipient was a 50-year-old woman who received a kidney transplant from the same donor. She was discharged on POD 6 and had no

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specific complaints. On POD 26, she reported dizziness, diplopia, and severe headache and was readmitted to the hospital. Fluid from a lumbar puncture culture showed *C. neoformans*. The serum CrAg titer was >1:2,560. The recipient was given amphotericin B lipid complex and 5-flucytosine. However, loss of consciousness and a convulsion occurred on POD 31. Further brain CT showed serious cerebral hemorrhage and compression of the brainstem. Her family withdrew care at that point, and the recipient died. Autopsy showed that the glomeruli of the transplanted kidney and spinal cord were infiltrated with oval-shaped yeast consistent with *C. neoformans*.

The recipients had negative clinical signs and no CrAg pretransplantation. However, the liver and kidney recipients who received organs from the same donor all showed development of cryptococcosis. *Cryptococcus* sp. in the blood culture and biopsies makes donor-derived transmission the most likely means of infection. Communication gaps between the microbiology laboratories and transplant team were associated with the donor-derived infection of our case. Positive blood culture results should be communicated immediately to initiate antifungal treatment promptly.

Although illnesses and deaths from donor-derived cryptococcosis remain high, results for these case-patients emphasize an increased pretransplant clinical awareness of donor-derived infection. Serum CrAg might identify infected donors and enable effective prophylaxis. In addition, timely communication of suspected results is critical to improve outcomes.

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M.S. and C.S. designed the methods, Y.T. and Q.X. conducted the study, M.S. and C.S. wrote the article, and Q.X. supervised the study.

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| Postoperative day | Cryptococcal antigen titer | Treatment                        |
|-------------------|----------------------------|----------------------------------|
| 30                | >1:2,560                   | Amphotericin B lipid complex and 5-flucytosine |
| 60                | >1:1,280                   | Oral fluconazole, 400 mg/d        |
| 90                | >1:640                     | Oral fluconazole, 400 mg/d        |
| 120               | 1:640                      | Oral fluconazole, 400 mg/d        |
| 180               | 1:128                      | Oral fluconazole, 400 mg/d        |
| 270               | 1:128                      | Oral fluconazole, 400 mg/d        |
| 360               | 1:32                       | Oral fluconazole, 400 mg/d        |
| 450               | Negative result            | Discontinued                     |
References

1. Penumarthi LR, La Hoz RM, Wolfe CR, Jackson BR, Mehta AK, Malinis M, et al. Cryptococcus transmission through solid organ transplantation in the United States: a report from the Ad Hoc Disease Transmission Advisory Committee. Am J Transplant. 2021;21:1911–23. https://doi.org/10.1111/ajt.16433

2. Singh N, Sifri CD, Silveira FP, Miller R, Gregg KS, Huprikar S, et al. Cryptococcosis in patients with cirrhosis of the liver and posttransplant outcomes. Transplantation. 2015;99:2132–41. https://doi.org/10.1097/TP.0000000000000690

3. Wang Y, Gu Y, Shen K, Cui X, Min R, Sun S, et al. Clinical features of cryptococcosis in patients with different immune statuses: a multicenter study in Jiangsu Province, China. BMC Infect Dis. 2021;21:1043. https://doi.org/10.1186/s12879-021-06752-x

4. Yuchong C, Fubin C, Jianghan C, Fenglian W, Nan X, Minghui Y, et al. Cryptococcosis in China (1985–2010): review of cases from Chinese database. Mycopathologia. 2012;173:329–35. https://doi.org/10.1007/s11046-011-9471-1

5. Chen M, Xu Y, Hong N, Yang Y, Lei W, Du L, et al. Epidemiology of fungal infections in China. Front Med. 2018;12:58–75. https://doi.org/10.1007/s11684-017-0601-0

6. Baddley JW, Forrest GN; AST Infectious Diseases Community of Practice. Cryptococcosis in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33:e13543. https://doi.org/10.1111/cstr.13543

7. Camargo JF, Simkins J, Schain DC, Gonzalez AA, Alcaide ML, Anjan S, et al. A cluster of donor-derived Cryptococcus neoformans infection affecting lung, liver, and kidney transplant recipients: Case report and review of literature. Transpl Infect Dis. 2018;20:e12836. https://doi.org/10.1111/tid.12836

8. Natarajan P, Lockhart SR, Basavaraju SV, Anjan S, Lindsley MD, McGrath MM, et al. Donor-derived Cryptococcus gattii sensu stricto infection in two kidney transplant recipients, southeastern United States. Am J Transplant. 2021;21:3790–4. https://doi.org/10.1111/ajt.16729

9. Malinis M, Boucher HW; AST Infectious Diseases Community of Practice. Screening of donor and candidate prior to solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33:e13548. https://doi.org/10.1111/cstr.13548

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Pulmonary Paragonimiasis in Native Community, Esmeraldas Province, Ecuador, 2022

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Paragonimiasis is a food-borne infection caused by several species of the Paragonimus fluke. Clinical manifestations can mimic tuberculosis and contribute to diagnostic delay. We report a cluster of paragonimiasis in a community in Ecuador, where active surveillance was set up after detection of the first 2 cases.

H uman paragonimiasis is a foodborne disease caused by trematode worms of the genus Paragonimus (1). Several species that have different geographic distributions have been associated with human infection (2). Paragonimiasis is caused by ingestion of raw/undercooked freshwater crabs or crayfish infested by metacercariae of Paragonimus species. Thus, it is frequently reported in Asia because of cultural dietary customs (1,3). Clusters are occasionally reported in Africa (4) and the Americas, where cases are observed mostly in countries in Latin America (5). Localized infection with P. kellicotti trematode occurs in the United States (1,5).

In Ecuador, cases have been reported from almost all provinces, but lack of official recording by the Ministry of Health and few active surveillance surveys probably cause an underestimation of the incidence (5). Nevertheless, Ecuador is considered the country with the highest incidence of paragonimiasis in South America (5). The main trematode species known to cause paragonimiasis in Ecuador is P. mexicana, although molecular characterization has not been performed extensively. Thus, information about circulating species might be incomplete (5,6).