

Donor-Derived Transmission of *Cryptococcus gattii* sensu lato in Kidney Transplant Recipients

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We describe cases of donor-derived transmission of *Cryptococcus deuterogattii* in 2 kidney transplant recipients in Brazil and published information on other cases. Prompt reduction of immunosuppression and initiation of antifungal therapy was required to successfully control the fungal infections and preserve engraftment.

After antiretroviral therapy for HIV patients was introduced, solid organ transplant recipients became one of the major risk groups for developing cryptococcosis, possibly transmitted from donors (1,2). We describe 2 cases of donor-derived transmission of *Cryptococcus deuterogattii* in Brazil. The donor in both of these cases was a 43-year-old man with an antemortem history of an unspecified brain tumor who had been declared brain dead after respiratory arrest.

Case-patient 1 was a 51-year-old man who received a kidney from the donor. Physicians initiated induction therapy with antithymocyte globulin and maintenance therapy with tacrolimus, prednisone, and azathioprine. On day 7 after the procedure, doctors performed a kidney biopsy after the patient experienced delayed graft function. Histopathology of the graft showed organisms consistent with *Cryptococcus* yeast cells, suggesting fungal pyelonephritis. The patient had no respiratory or neurologic complaints. Results from his laboratory tests showed 7,000 leukocytes/mm³, 201,000 platelets/ μ L, serum

creatinine 13.29 mg/dL, and serum urea 132 mg/dL. Brain and thorax radiographs revealed no abnormalities. Results of a lumbar puncture showed an opening pressure of 18 cm H₂O, 2 leukocytes/mm³, protein 63 mg/dL, and glucose 77 mg/dL; a *Cryptococcus* antigen latex (CrAg-latex) agglutination test result was positive (titer 1:8). Blood and urine cultures indicated *Cryptococcus* species, and the serum CrAg-latex agglutination test result was positive (titer 1:1,024).

After the diagnosis of cryptococcosis in the first patient, a 59-year-old woman (case-patient 2) who had received a kidney from the same donor was contacted for evaluation. Physicians had initiated induction therapy with antithymocyte globulin and maintenance therapy with tacrolimus, prednisone, and mycophenolic acid. She was discharged on day 8 after the procedure and was asymptomatic when recalled on day 10. Clinicians performed blood and urine cultures, radiographs of the chest and the brain, and a lumbar puncture. The radiograph revealed no abnormalities. Results of lumbar puncture showed opening pressure of 15 cm H₂O, 3 leukocytes/mm³, protein 35 mg/dL, and glucose 174 mg/dL. Results of India ink and CrAg-latex agglutination tests were positive (titer: 1:64). Blood cultures and a urine sample indicated *Cryptococcus* species. No fungal growth was detected in a cerebrospinal fluid sample. The serum CrAg-latex agglutination was positive (titer 1:1,024).

A revised histology of the brain biopsy of the donor showed yeasts of *Cryptococcus* species that had not been detected previously. Results of a CrAg-latex agglutination test performed on a stored serum sample from the donor was positive (titer: 1:1,024). To rule out infection by *Cryptococcus* species in the organ recipients prior to the transplantations, CrAg-latex agglutination tests were performed on stored pretransplant serum samples from both recipients; results for both were negative.

Both patients were treated with amphotericin B lipid complex (5 mg/kg 1 \times /d for 21 d) in combination with 5-fluorocytosine (25 mg/kg 4 \times /d for 14 d); dosages of immunosuppressive drugs were lowered. Therapy was switched to intravenous fluconazole (400 mg/d) after results of blood and urine cultures became negative. After clinical and microbiological remission of the infection, dosage was adjusted on the basis of renal function to 300 mg/d of oral fluconazole and was maintained for 2 years. Three years after stopping all antifungal therapy, no relapse of cryptococcosis was documented.

All 6 isolates from the recipients were characterized at a reference laboratory at Universidade Federal de São Paulo (São Paulo, Brazil) and sent to Canisius-Wilhelmina Hospital (Nijmegen, The Netherlands). We performed AFLP (amplified fragment length polymorphism) fingerprinting and multilocus sequencing typing, which showed that all isolates were *C. deuterogattii* genotype AFLP6/VGII. The revision of slides from formalin-fixed paraffin-embedded

tissue blocks from donor brain biopsies showed *Cryptococcus* yeasts. We performed fungal DNA extraction and amplified parts of *CAP59*, *GPD1*, *IGS1*, *LAC1*, *PLB1*, *SOD1*, and *URA5* loci (2). Phylogenetic analysis showed genetic similarity between the *C. deuterogattii* isolates from the kidney recipients and those from the donor's brain (Figure).

We searched the literature for other cases of fungal infections from solid organ donors in transplant

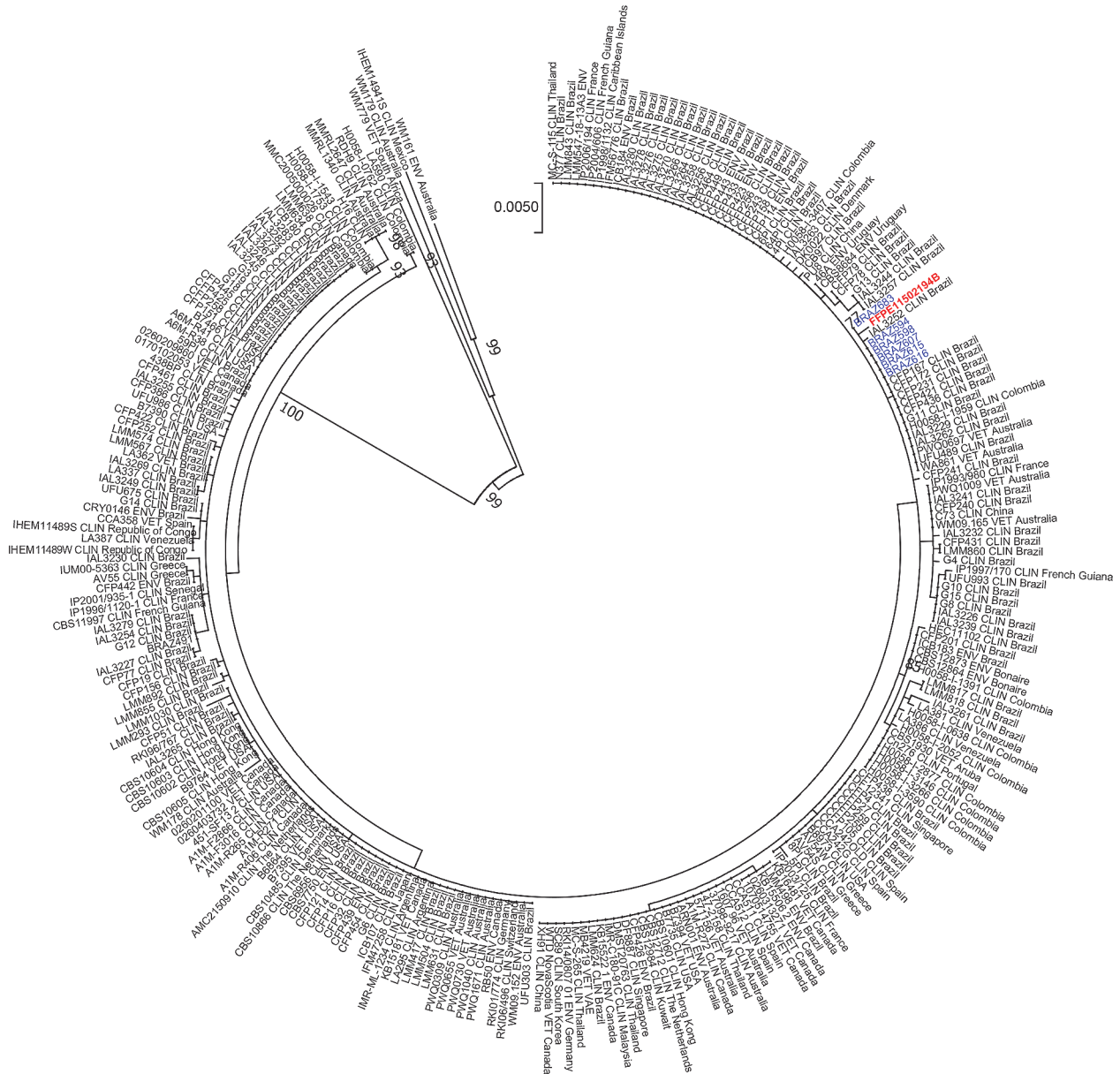


Figure. Phylogenetic maximum-likelihood analysis of 6 *Cryptococcus deuterogattii* isolates from 2 kidney transplant recipients in Brazil (blue), the organ donor (red), and cases from the literature (Appendix, <https://wwwnc.cdc.gov/EID/article/26/6/19-1765-App1.pdf>), along with reference isolates. Isolates from the 2 transplant recipients came from blood and urine; the genetic material from the donor came from a formalin-fixed paraffin-embedded brain tissue block. The GenBank accession numbers are KU642696-KU642701 (*CAP59*), KU642741-KU642746 (*GPD1*), KU642786-KU642791 (*IGS1*), KU642831-KU642836 (*LAC1*), KU642876-KU642881 (*PLB1*), KU642967-KU642972 (*SOD1*) and KU642921-KU642926 (*URA5*). Tree represents 1,000x bootstraps. Scale bar represents substitutions per site.

recipients and found 12 additional cases of presumed or confirmed donor-derived cryptococcosis (Appendix, <https://wwwnc.cdc.gov/EID/article/26/6/19-1765-App1.pdf>). Molecular identification was provided in only 6 out of 14 graft recipients (3–10). On the basis of the 2 cases we describe and data from the literature review, we suggest the following procedures for effective clinical management: performing blood and urine cultures, radiograph of the lungs and brain, and lumbar puncture to rule out dissemination; reducing immunosuppression to control infection; promptly initiating induction combination therapy with an amphotericin B lipid complex and 5-fluorocytosine; preserving the infected engraftment, if possible, in the absence of large fungal masses and abscesses; and extending the length of antifungal therapy when fungal elements persist in tissues.

In conclusion, we found that *C. deuterogattii* may be transmitted by infected allografts, representing a medical concern in countries to which *C. gattii* species complex is endemic. Cryptococcosis incidence might be reduced by excluding organ donor candidates with a history of neurologic disease without a clear definition of its etiology. Ensuring that clinicians are trained to recognize and treat this fungal infection would likely further reduce transmission from donors.

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Appendix

Appendix Table. Demographic, clinical, and transplant data of donor-derived transmission of confirmed and presumed *Cryptococcus* spp. in solid organ transplantation

| Reference no. Sex/age of recipient Type of transplant Transmission category | Characteristics of the donor | Time to infection diagnosis after transplant | Clinical and laboratorial findings of recipient's fungal diagnosis | Treatment | Outcome |
|--|---|--|---|---|---|
| NA (case 1 this study) M/51 y Kidney, deceased donor Confirmed transmission | M/43 y with unspecified brain tumor diagnosed before death. Autopsy showed brain cryptococcoma. FFPE material subjected to molecular testing, which identified <i>C. deuterogattii</i> . | 7 d | Delayed graft function and hemodialysis. Blood and urine cultures yielded <i>C. deuterogattii</i> . CSF positive for cryptococcal antigen (1:8) | Lipid complex AMB plus 5-FC, switched to oral FLU | Alive |
| NA (case 2 this study) F/59 y Kidney, deceased donor Confirmed transmission | M/43 y with unspecified brain tumor diagnosed before death. Autopsy showed brain cryptococcoma. FFPE material subjected to molecular testing, which identified <i>C. deuterogattii</i> . | 10 d | Asymptomatic. Blood and urine cultures yielded <i>C. deuterogattii</i> . CSF positive for cryptococcal antigen (1:64) | Lipid complex AMB plus 5-FC, switched to oral FLU | Alive |
| (3) F/29 y Kidney, deceased donor Confirmed transmission | M/43 y with presumed diagnosis of brain tumor and intracranial hypertension. Donor kidney not transplanted showed 2 cryptococcal granulomas. | 5 d | Asymptomatic. Urine culture yielded <i>Cryptococcus</i> spp. Chest radiograph was normal, CSF testing was not performed. | Conventional AMB plus 5-FC | Alive at 10 wk after transplant, negative urine cultures |
| (4) F/8 y Cornea, deceased donor Confirmed transmission | F/25 y with polymyositis. Persistent fever, died due to progressive respiratory failure. Blood cultures yielded <i>C. neoformans</i> . Postmortem exam revealed generalized cryptococcosis. | 2 mo | Decreased visual acuity with a 3 mm yellow-white mass in anterior chamber. Aqueous fluid with positive culture for <i>C. neoformans</i> and a positive antigen (1:512) | Topical and systemic conventional AMB and 5-FC for 6 wk | Alive at 2 months after transplant, better light perception, only residual corneal clouding in affected eye |
| (5) F/24 y Lung, deceased donor Presumed transmission | Not reported | 2 d | 2 d after operation, recipient had fever, leukocytosis, and hypoxemia. Endotracheal cultures yielded <i>C. neoformans</i> . Serum cryptococcal antigen and blood cultures were negative. CSF testing was not performed. | FLU (400 mg/day) for 4 mo | Alive at 12 mo after transplant |
| (6) F/69 y Cornea, deceased donor Presumed transmission | F/58 y | 7 mo | Persistent corneal button edema that required sutures 5 d after operation. The edema persisted and 9 mo later second corneal transplant was performed by removing the corneal | Curative surgery | Alive and cured after the 2nd corneal transplant |

| Reference no. Sex/age of recipient Type of transplant Transmission category | Characteristics of the donor | Time to infection diagnosis after transplant | Clinical and laboratorial findings of recipient's fungal diagnosis | Treatment | Outcome |
|--|--|--|---|--|---|
| (7) Recipient 1: F/72 y Liver, deceased donor Confirmed transmission | F/51 y with sarcoidosis. Headache, slurred speech and hydrocephalus. Autopsy available after 30 d after transplant showed meningoencephalitis by <i>C. neoformans</i> . | 2 wk | Gastrointestinal bleeding and immune thrombocytopenic purpura. Histopathology of liver and spleen showed <i>Cryptococcus</i> spp. Blood cultures, liver and spleen tissues yielded <i>C. neoformans</i> . CSF testing was not performed. | Lipid formulation of AMB for 8 wk, switched to FLU | Death due to aspiration pneumonia 6 mo after transplant |
| (7) Recipient 2: M/58 y Kidney, deceased donor Confirmed transmission | F/51 y with sarcoidosis. Headache, slurred speech and hydrocephalus. Autopsy available after 30 d after transplant showed meningoencephalitis by <i>C. neoformans</i> . | 16 d | Fever, malaise. Blood cultures yielded <i>C. neoformans</i> and serum cryptococcal antigen (1:256). CSF analysis was normal with cryptococcal antigen negative. Chest radiograph was performed showing focal consolidation and effusions. | Lipid formulation of AMB and 5-FC for 14 d switched to FLU | Alive for 6 mo with oral FLU |
| (7) Recipient 3: M/46 y Kidney, deceased donor Confirmed transmission | F/51 y with sarcoidosis. Headache, slurred speech and hydrocephalus. Autopsy available after 30 d after transplant showed meningoencephalitis by <i>C. neoformans</i> . | 24 d | Fever, neck stiffness, and photophobia. CSF and blood cultures yielded <i>C. neoformans</i> . | Lipid formulation of AMB and 5-FC for 17 d switched to FLU | Alive for 6 mo with oral FLU |
| (8) M/50 y Kidney, deceased donor Confirmed transmission | Donor died of presumed bacterial meningitis. <i>C. neoformans</i> yielded from donor CSF and blood after the transplant. | 9 wk | Nausea, vomiting, severe headache, coughing, and respiratory effort. CSF cultures yielded <i>C. neoformans</i> and CSF cryptococcal antigen was positive. | Liposomal AMB and intravenous 5-FC for 3 wk, switched to oral FLU | Alive for 9 mo with oral FLU |
| (9) F/63 y Liver, deceased Donor Presumed transmission | M/48 y with severe intracranial hemorrhage. CSF testing was not performed. | ≤1 wk | Dyspnea and respiratory failure, fever, and rising bilirubin. Blood cultures yielded <i>C. neoformans</i> and serum antigen serum was positive (1:2048). Serum cryptococcal antigen test before transplant was negative. | Conventional AMB followed by liposomal AMB for 4 wk, switched to oral FLU | Alive for 1.5 y after transplant |
| (10) Recipient 1 F/42 y Lung, deceased donor Confirmed transmission | M/55 y with nausea, vomiting, mental status deteriorated and brain death. Radiograph of the chest revealed right lobe infiltrate. 5 d after transplant blood and BAL cultures yielded <i>C. neoformans</i> . | Immediately after operation | Fever. Recipient's BAL culture yielded <i>C. neoformans</i> . Blood culture and serum cryptococcal antigen were negative. | VOR ≤90 d after transplant, switched to lipid complex AMB for 12 d, on discharge switched to POS | Alive for ≥10 mo, negative BAL cultures |
| (10) Recipient 2 M/77 y Kidney, deceased donor Confirmed transmission | M/55 y with nausea, vomiting, mental status deteriorated and brain death. Radiograph of the chest revealed right lobe infiltrate. 5 d after transplant blood and BAL cultures yielded <i>C. neoformans</i> . | 67 d | Fever, weakness, gait disturbance, and confusion. CSF positive for cryptococcal antigen (1:1280) and CSF positive culture for <i>Cryptococcus</i> spp. | Lipid complex AMB plus 5-FC, switched to oral FLU | Alive |

| Reference no. | Sex/age of recipient | Time to infection diagnosis after transplant | Clinical and laboratorial findings of recipient's fungal diagnosis | Treatment | Outcome |
|---------------|--|--|--|-----------------------------|---|
| (10) | M/55 y | 106 d | Dizziness, headache, diplopia, blurred vision, and gait disturbance. Blood and CSF cultures yielded <i>C. neoformans</i> . | Lipid complex AMB plus 5-FC | Death due to complications from intracranial hypertension |
| | M/58 y | | | | |
| | Liver, deceased donor | | | | |
| | Confirmed transmission | | | | |
| | Characteristics of the donor | | | | |
| | M/55 y with nausea, vomiting, mental status deteriorated and brain death. Radiograph of the chest revealed right lobe infiltrate. 5 d after transplant blood and BAL cultures yielded <i>C. neoformans</i> . | | | | |

*References provided in the main text of the article. CSF, cerebrospinal fluid; FFPE, formalin-fixed paraffin-embedded; NA, not applicable; 5-FC, 5-fluorocytosine; AMB, amphotericin; FLU, fluconazole; POS, posaconazole; VOR, voriconazole.