

Brief Report

TRANSMISSION OF *HISTOPLASMA*
CAPSULATUM BY ORGAN
TRANSPLANTATION

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HISTOPLASMOSIS may occur either after primary infection or after reactivation of latent infection, and its incidence among immunocompromised persons, including recipients of organ transplants, is increasing.¹⁻³ A variety of infectious agents are known to be transmissible by organ transplantation,⁴ but there has been no definitive evidence of transmission of *Histoplasma capsulatum* by this route. In the few previous reports of possible cases of such transmission, neither reactivation of latent infection nor primary infection from an environmental source was definitively ruled out.⁵⁻⁸

Recently, molecular typing of *H. capsulatum* has been shown to be useful in distinguishing relapse from reinfection among patients infected with the human immunodeficiency virus who have recurrent histoplasmosis^{9,10} and in defining the likely source of the infection in areas where histoplasmosis is not endemic.¹¹ Furthermore, molecular typing of *H. capsulatum* by the random amplified polymorphic DNA-polymerase chain reaction (RAPD-PCR) method is able to discriminate among clinical isolates, even those that are restricted to small geographic areas, making it a useful tool for epidemiologic investigation.¹⁰⁻¹²

We report the use of this technique for investigating the disseminated histoplasmosis that developed in two recipients of cadaveric organ transplants from the same donor, who had lived in an area where histoplasmosis is highly endemic. The two recipients lived in different states, received their transplants through different programs, and had no known epidemiologic relation to each other. Neither of the transplant recipients had ever resided in or visited an area where histoplasmosis

is endemic. However, both had received an organ from the same donor, who had resided in an area where histoplasmosis is endemic. An epidemiologic investigation was performed, and *H. capsulatum* isolates from the two recipients were analyzed by RAPD-PCR molecular typing and compared with *H. capsulatum* isolates from epidemiologically unrelated patients.

CASE REPORTS

Recipient 1

A 31-year-old man received a cadaveric kidney transplant because of end-stage renal disease resulting from chronic reflux nephropathy. He had been born and raised in Montana, and his only travel outside the state was to Washington to receive his kidney transplant. His course after the transplantation was complicated by esophagitis associated with herpes simplex virus infection. His immunosuppressive medications included prednisone, tacrolimus, and mycophenolate mofetil. Eight months after transplantation, he was admitted to a hospital in Montana for evaluation of fever, weight loss, and pancytopenia. An extensive clinical investigation was conducted, and lysis-centrifugation cultures of blood ultimately grew *H. capsulatum*, confirming the diagnosis of disseminated histoplasmosis. Treatment with amphotericin B resulted in resolution of the fever and pancytopenia. Serum samples that had been obtained before transplantation showed no evidence of antibodies to *H. capsulatum*.

Given the absence of known risk factors for histoplasmosis in this patient, the possibility of allograft-transmitted infection was raised, and an investigation of the donor and of other potential recipients was initiated. The local organ-procurement agency was contacted, as were all other recipients of organs and tissue from the same donor.

Recipient 2

The organ-procurement agency reported that the other kidney from the donor of the kidney given to Recipient 1 had been transplanted into another patient, in a different state. The second transplantation program was contacted.

The second recipient was a 44-year-old man who had received a cadaveric kidney transplant for end-stage renal disease due to Berger's disease (also called IgA nephropathy). The patient had been born and raised in Oregon and had never visited an area where *H. capsulatum* infection was known to be endemic. The patient's immunosuppressive medications included prednisone, tacrolimus, and azathioprine. Nine months after transplantation (shortly after the diagnosis of disseminated histoplasmosis in Recipient 1), the patient was admitted to a hospital in Oregon for the evaluation of fever, weight loss, and pancytopenia. After an extensive diagnostic evaluation, *H. capsulatum* was recovered from cultures of his blood and bone marrow. The patient's condition responded to therapy with amphotericin B. Serum samples that had been obtained before the transplantation showed no evidence of antibodies to *H. capsulatum*. There had been no known contact, direct or indirect, between Recipient 1 and Recipient 2, except for the receipt of an organ transplant from the same donor.

Recipient 3

A 60-year-old man with cirrhosis associated with alcohol consumption and hepatitis C virus infection had received a cadaveric liver transplant from the donor who provided kidneys to Recipients 1 and 2. His immunosuppressive medications included prednisone and tacrolimus. Although this patient was asymptomatic, he was evaluated for possible subclinical *H. capsulatum* infection because of the diagnosis of disseminated histoplasmosis in the other two recipients of organs from the same donor. Lysis-centrifugation cultures of blood were negative, as were the results of serologic studies, urine antigen studies, and blood antigen studies. No evidence of clinical histoplasmosis has appeared during three years of follow-up.

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Donor

The organ donor was a 41-year-old man who had sustained severe head and chest injuries in a motor vehicle accident while visiting Montana. His permanent residence was in Kansas City, Kansas, an area where histoplasmosis is highly endemic. He was declared brain-dead, and his family consented to organ donation. At the time of organ procurement, the liver and both kidneys appeared grossly normal, and they were eventually transplanted into the three recipients described above. No other organs or tissues were used for transplantation.

METHODS

Isolates from the available cultures from Recipient 1 (blood) and Recipient 2 (blood and bone marrow) were analyzed by RAPD-PCR according to previously described methods, with primers H1, H2, and H3.¹² The three isolates were compared with seven control isolates of *H. capsulatum* obtained from epidemiologically unrelated patients throughout the United States, including the Indianapolis area, and the isolates were also compared with a standard laboratory strain (G217b [American Type Culture Collection 26032]). Serum samples obtained before and after transplantation from the three recipients and a serum sample from the donor obtained at the time of organ procurement were tested for antibodies to *H. capsulatum* by complement fixation, as previously described.¹³ A complement-fixation titer of 1:8 or greater was considered positive.¹

RESULTS

Analysis of pretransplantation serum samples showed that none of the three organ-transplant recipients had evidence of prior infection with *H. capsulatum* (Table 1). The donor, however, had a positive titer (1:16) of complement-fixing antibodies to the yeast-phase antigens of *H. capsulatum*, a finding consistent with either current infection or infection within the previous several years.¹⁴

The DNA-fingerprint patterns of the *H. capsulatum* isolate from the blood of Recipient 1 and of the isolates from the blood and bone marrow of Recipient 2 were identical, according to RAPD-PCR analysis with the use of primers H1, H2, and H3 (Fig. 1A). Furthermore, the DNA patterns of the isolates from Recipients 1 and 2, amplified with primer H1, differed from those of the *H. capsulatum* isolates from epidemiologically unrelated patients, each of which

was genetically unique, and from the G217b strain (Fig. 1B).

DISCUSSION

The epidemiologic circumstances, including the absence of risk factors for histoplasmosis in the two transplant recipients, combined with the results of molecular typing, strongly support the hypothesis that *H. capsulatum* was transmitted to these two geographically separated patients by the transplantation of kidneys from a single donor. However, the data do not allow us to define the precise mechanism of transmission. The donor may have had a recent disseminated infection involving the kidneys or, alternatively, may have had a latent renal infection as a result of a primary infection at a distant site. The latter possibility is more likely, since the donor had been healthy before his accident, and since at the time of organ procurement he had only a low titer of antibodies to histoplasma antigens and had no clinical evidence of disseminated histoplasmosis.

Interestingly, although *H. capsulatum* has generally been considered to establish latency primarily in organs replete with reticuloendothelial cells (such as the liver), in this instance the organism was transmitted only to the two kidney-transplant recipients and not to the liver-transplant recipient. The three recipients received a similar degree of immunosuppressive therapy, and none received any systemic prophylaxis against fungal infection. Symptomatic histoplasmosis involving the kidneys, occasionally in the absence of systemic involvement, has previously been reported.^{1,15-18} It is possible that subclinical renal involvement is more common than is recognized and that the kidneys represent another potential site of latency after primary infection with *H. capsulatum*.

Although the incidence of histoplasmosis among organ-transplant recipients in areas where *H. capsulatum* infection is endemic is increasing, it is uncertain whether primary infection or reactivation of la-

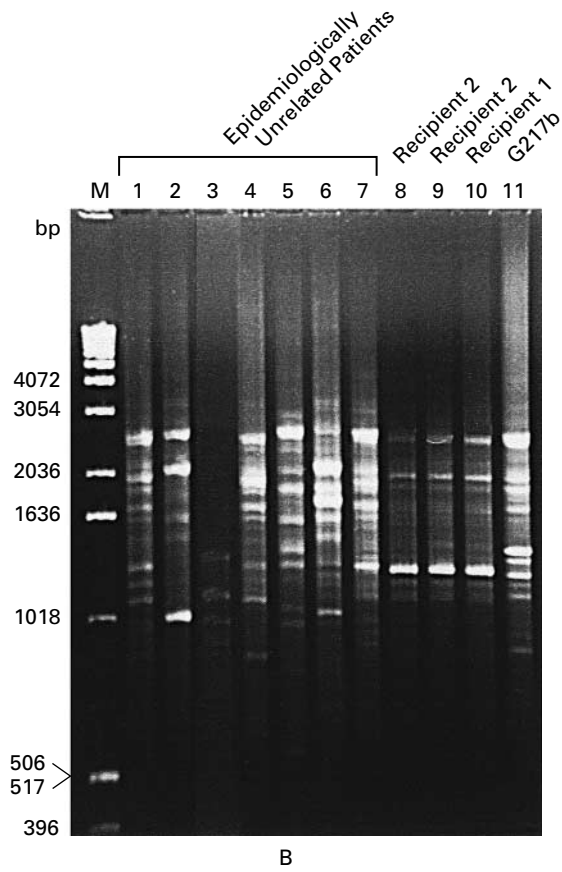
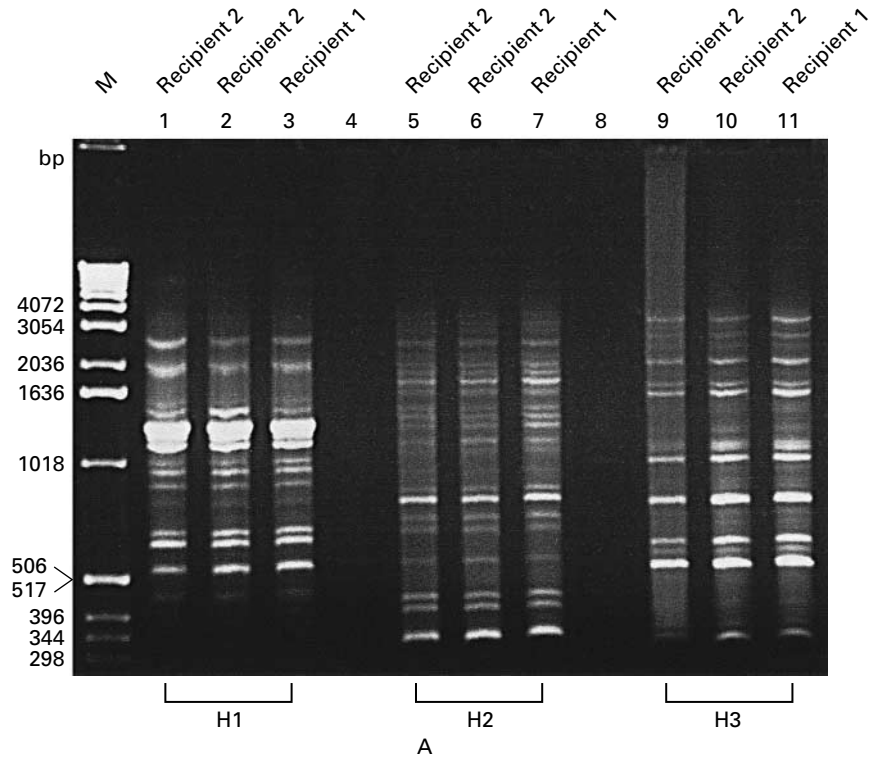
TABLE 1. RESULTS OF SEROLOGIC TESTING FOR COMPLEMENT-FIXING ANTIBODIES TO THE YEAST-PHASE OR MYCELIAL-PHASE ANTIGENS OF *H. CAPSULATUM*. *

PATIENT	BEFORE TRANSPLANTATION		AFTER TRANSPLANTATION	
	YEAST	MYCELIA	YEAST	MYCELIA
Donor	1:16	<1:8	—	—
Recipient 1	<1:8	<1:8	1:32	<1:8
Recipient 2	<1:8	<1:8	1:16	<1:8
Recipient 3	<1:8	<1:8	<1:8	<1:8

*A complement-fixation titer of $\geq 1:8$ was considered positive.¹

Figure 1 (facing page). DNA-Fingerprint Patterns of *H. capsulatum* Isolates from Two Recipients of Organs from the Same Donor.

As shown in Panel A, the results of RAPD-PCR analysis of isolates from blood and bone marrow from Recipient 2 and of an isolate from blood from Recipient 1 are identical. Isolates were amplified with primers H1, H2, and H3. In each pair of lanes for isolates from Recipient 2, the first is from blood and the second is from bone marrow. Lanes 4 and 8 show water controls. Panel B shows the results of RAPD-PCR analysis of seven control isolates from blood or bone marrow, isolates from blood (lane 8) and bone marrow (lane 9) from Recipient 2, an isolate from blood from Recipient 1, and reference strain G217b (lane 11), amplified with primer H1. Each control isolate is genetically unique, whereas those from Recipients 1 and 2 are identical. Lane M shows standard molecular-weight markers.



tent infection is the more common mechanism. The increased incidence of infection among organ-transplant recipients during outbreaks of histoplasmosis in such areas^{1,2} suggests that primary infection may be an important mechanism of acquisition. Furthermore, the presence of antibodies to *H. capsulatum* before transplantation does not appear to predict the subsequent development of histoplasmosis in organ-transplant recipients; this too suggests that reactivation may be a less likely mechanism than primary infection.¹⁹ To our knowledge, however, the incidence of primary infection acquired by organ transplantation has never been studied.

Cases of histoplasmosis transmitted directly by organ transplantation may not be recognized, given the increased background incidence of infection among organ-transplant recipients residing in areas where the disease is endemic. In addition, as our cases illustrate, infections transmitted by organ transplantation can become clinically apparent relatively late after transplantation, further decreasing the likelihood of suspicion that the infection may have been acquired from the transplanted organ. Epidemiologic studies should be undertaken to determine whether transmission by transplantation of infected organs is an under-recognized mechanism of acquisition of *H. capsulatum* in areas where the infection is endemic.

These findings also have implications for clinicians who care for organ-transplant recipients. Obtaining a history of the patient's places of residence to determine whether he or she has lived in areas where infections with geographically restricted fungi are endemic is part of the routine evaluation of an organ-transplant recipient when such an infection is suspected. As our report illustrates, obtaining such information about the donor may also be helpful in selected cases. The fact that the two kidney recipients in whom disseminated histoplasmosis developed received their organs from different transplantation programs in different states further complicated early recognition of transplant-transmitted infection in this instance. As organ-preservation techniques continue to improve, there will probably be an even wider geographic distribution of organs, making such recognition even more difficult. A system for notification, surveillance, and tracing in cases of possible donor-transmitted infection might help in the recognition of such infections in the future.

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