Case Report

Donor-Derived *Cryptococcus* Infection in Liver Transplant: Case Report and Literature Review

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Abstract

Cryptococcosis occurring within 30 days after transplant is unusual. We present a case of cryptococcosis diagnosed within 2 weeks of liver transplant and cryptococcal infection transmitted by liver transplant is considered as the cause.

A 63-year-old woman with hepatitis C virus-related cirrhosis and hepatocellular carcinoma had an orthotopic liver transplant from a 45-year-old donor. The immediate postoperative course was smooth, although she was confused with a fever, tachycardia, respiratory failure of 1 week's duration after the orthotopic liver transplant. A liver biopsy was performed for hyperbilirubinemia 2 weeks after the orthotopic liver transplant that showed a *Cryptococcus*-like yeast. Her blood culture was re-examined, and it was confirmed as *Cryptococcus* neoformans that had been misinterpreted as candida initially. At the time of the re-examination, her sputum was clear. We checked her preoperative blood sample, retrospectively, for serum cryptococcal antigen with negative result. She was on liposomal amphotericin treatment for 1 month when her blood culture became negative. She was discharged home, with good liver function and a low antigen titer for cryptococcal infection.

Cryptococcal disease usually develops at a mean of 5.6 months after transplant. However an early occurrence is rare. Apart from that, its variable clinical presentations make early detection difficult. It might be an early reactivation or a donor-derived infection. The latter usually occurs in unusual sites (eg, the transplanted organ as the sole site of involvement). Our case presented as cryptococcoma and liver involvement was diagnosed by an unintentional liver biopsy.

Key words: *Donor-derived,* Cryptococcus *infection, Liver transplant, Early onset cryptococcosis, Liver involvement*

Introduction

Cryptococcosis is a systemic mycosis caused by the encapsulated yeasts *Cryptococcus neoformans* and *Cryptococcus gattii*, organisms found in soil and often associated with pigeon droppings. The incidence of cryptococcosis is increased in immunocompromised patients, and cryptococcosis is considered an opportunistic fungal infection. Cryptococcosis is the third most-common fungal infection in solid-organ transplant recipients.[1-3] Usually, the disease occurs more than 1 year after transplant, and it is usually considered reactivation of latent infection.[4,5]

In most cases, although acquisition of the organism occurs via inhalation, there is risk of transmission through donor organs. Usually, it presents as early-onset cryptococcosis. But it is difficult to determine whether it is donor-derived or an early reactivation, unless the donors can be traced and show evidence of cryptococcosis. Early-onset cryptococcosis in a solid-organ transplant is rare; it has been reported only in 12 patients.[6,7] Additionally, transmission of cryptococcosis via donor solid organs is unusual, and only 10 patients had been reported.[6-9] We present a liver transplant recipient with cryptococcal infection identified in a biopsy specimen of a liver done for

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hyperbilirubinemia. The infection was seen as a donor-derived transmission, as the native liver biopsy and cryptococcal antigen test in recipient were negative for cryptococcal infection. They manifested as an early-onset disease at an unusual site (the liver).

Case Report

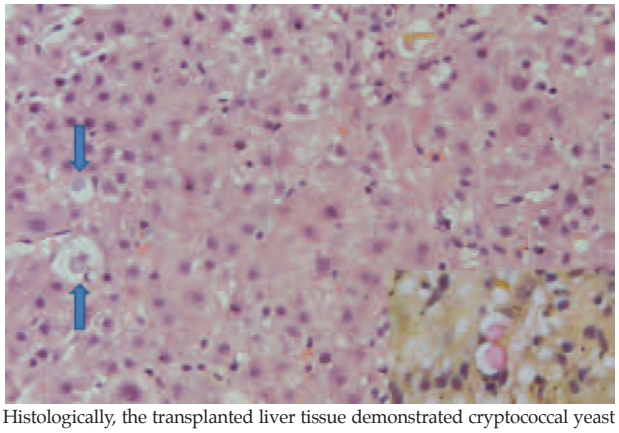
A 48-year-old man had a previous history of with a history of intracranial hemorrhage, with a coma, was sent to our emergency department. On admission, a chest radiograph showed no infiltrates or other active lesions. A brain computed tomographic scan revealed a massive hemorrhage in left thalamus and ventricles. No definitive findings, except on admission, positive Venereal Disease Research Laboratory test was seen in blood drawn. The results of a lumbar puncture and cerebrospinal fluid studies were not obtained. The patient was pronounced "brain-dead"; and his organs were made available for donation after passing a brain death test. All protocols were approved by the ethics committee of our institution and conformed with the ethical guidelines of the 1975 Helsinki Declaration.

His liver was donated to, and transplanted in, a 63-year-old woman with hepatitis C-related cirrhosis complicated with massive ascites and hepatocellular carcinoma. Before transplant, massive ascites in the recipient were so severe that they were associated with uterine prolapse and bilateral hydronephrosis owing to downward stretching of the internal organs by a tense abdomen.

About one and half months before her transplant, she got skin rashes on her both legs, probably because of an allergy, which quickly progressed to multiple skin erosions. Because at that time, she was on a low-dose steroid therapy for multiple allergic rashes and erosions on both legs about 1 month before the transplant. Because the donor's serology test was positive for Venereal Disease Research Laboratory, she was given penicillin G for prophylaxis to prevent transmission of syphilis to her. She was extubated immediately, and her postoperative course was uncomplicated, and she was weaned off the ventilator postoperative day (POD) number 2. Her pretransplant total bilirubin was only 18.81 μmol/L and went up gradually from 107.73 μmol/L on POD 1 to 196.65 mmol/L on POD 6. She had dyspnea and became agitated on POD 5; her temperature rose to 38.5°C, she went into respiratory failure, and was re-intubated on POD 6. She was given fluconazole (400 mL/d) beginning on POD 9 for *candida tropicalis*, which was isolated in a blood culture.

She had persistently high bilirubin around 171 μmol/L, for which a liver biopsy was done on POD 14, and few *Cryptococcus*-like encapsulated yeast were found incidentally (Figure 1). Nothing was found in her native liver and or pretransplant donor liver biopsy. Knowing that, her transplanted liver was infected with *Cryptococcus*-like yeast, a blood culture taken on POD 14 was re-examined carefully, which also grew *Cryptococcus neoformans* was confirmed.

Figure 1. Transplanted Liver Tissue



Histologically, the transplanted liver tissue demonstrated cryptococcal yeast within the hepatic parenchyma (arrows), (hematoxylin and eosin stain, ×400). The cryptococcal capsules were stained red in mucicarmine stain (left lower inset).

Pathogenic *C. neoformans* was isolated primarily by repeated growth and identifying yeasts from multiple, consecutive blood cultures, subcultured, using streaking clinical specimens of Sabouraud dextrose agar. *Cryptococcus neoformans* grows at 37°C (98.6°F), assimilates inositol, produces urease, and does not produce mycelia on cornmeal agar. *Cryptococcus neoformans* also produces melanin when incubated on agar that contains seeds from the common weed *Guizotia abyssinica*. Her serum cryptococcal antigen titer in serum was also positive for 1:2048, though her sputum was negative for cryptococcal infection, but only the pseudomonas species. A retrospective examination of her preoperative blood sample for cryptococcal antigen, however, was negative.

A significant conscious disturbance with poor motor activity was noted on PODs 15 and 16. She had been on amphotericin B (40 mL/d IV) since POD 21, and was shifted to liposomal amphotericin B from POD 30 for another 19 days (for a total of 4 weeks). Her condition improved, with a gradual decline of her bilirubin to normal with negative blood cultures.

Antifungal treatment was shifted to oral fluconazole before she was discharged home. During the out-patient clinic follow-up, her *Cryptococcus* antigen titer decreased gradually to positive in 1:1024 six months after transplant, and only positive in 1:32 at 1 year, and 1:16 at 1 year and a half after the transplant. Because there was no evidence of active infection, the fluconazole was discontinued after 1 year, and the patient was followed-up regularly without recurrence until now (1.5 years after transplant).

Discussion

Hyperbilirubinemia has been reported as a manifestation in cryptococcosis disease in several case reports.[10-12] The diagnosis of the cryptococcosis in our case was discovered in the liver biopsy, and found incidentally during a work-up for high bilirubin. Our patient had already been taking fluconazole for candidemia since POD 9, and her second blood culture was initially diagnosed as candidemia. The liver biopsy led to a diagnosis of cryptococcosis; otherwise, the woman might have been misdiagnosed and given an ineffective treatment, or there would have been a delay in the diagnosis, without timely treatment, followed by severe morbidity or death.

It is rare in clinical practice to see cryptococcosis presents so early after a transplant. Cryptococcosis causes up to 8% of all fungal infections in solid-organ transplant patients, third after *Candida* and *Aspergillus* species,[1-3] but usually presents late (>1 year) after transplant. In a recent surveillance study of cryptococcosis among recipients of solid-organ transplant patients, the median onset was 575 days after the transplant, with 75% of cases occurring < 3 years after the transplant.[3] Most posttransplant cryptococcosis is considered a reactivation of latent or quiescent infection in the recipient.[4]

In a Saha and associates study, pretransplant serum samples for cryptococcal-specific antibodies showed that 52% of the solid-organ transplant recipients with cryptococcosis exhibited serologic evidence of infection before the transplant.[13] In patients with prior antibody reactivity who developed cryptococcal infection disease significantly soon after the transplant compared with those without pre-existing reactivity, but median time to onset of disease in these patients was still 5.6 months.[13]

In our recipient, transmission from the donor was therefore considered for the disease, as the results for her pretransplant serum sample for cryptococcal-specific antibodies and liver biopsy were negative. Because of the shortage of supply for, more marginal and high-risk donors are being used currently. Although the incidence of unexpected donor-derived infections are low, detection before an organ donation, or early detection after transplant, before a recipient's progression of clinical symptoms progresses to the point where it is impossible for successful is fundamental for successful treatment.

Donor evaluation to identify transmissible infections is important but is often limited by laboratory technology at specific institutions, and requiring that they finish many medical, social, and legal procedures in a time short time before the transplant. At present, there is no pretransplant donor screening guideline for cryptococcal infection disease. Pretransplant screening with serologic tests or cultures is currently not routinely recommended. However, a carefully taken history from the donor including the location of residence, and any fever, headache, or unexplained mental abnormality may help to determine whether more, there-detailed preoperative evaluation, which includes these geographically restricted fungi (especially in high-risk donors).

Although candidemia occurs more commonly than cryptococcemia early after the transplant, "yeast isolates" in the blood cultures should be carefully interpreted because the preferred treatment for cryptococcosis in the transplanted patient is using a lipid formulation of amphotericin B_2, because many transplant recipients may already have to avoid a worsening of renal function who are already on dysfunction and may be receiving other nephrotoxic agents (eg, calcineurin inhibitors) or antibiotics (eg, vancomycin).

A lumbar puncture has been suggested to determine if there is neurologic involvement or not,[2] because mortality in solid-organ transplant recipients with cryptococcosis range from 33% to 42% and may be as high as 49% in those with central nervous system disease.[1] Overall mortality in solid-organ transplant recipients with cryptococcosis currently is about 14%.[14] In our case, we did not perform a lumbar puncture was fortunately. Fortunately, this life-threatening infection was diagnosed early by a liver biopsy, and was successfully treated.

To detect *Cryptococcus* infection in perioperative period peritransplant recipients is critical. In the study by Sun and associates, early-onset posttransplant

cryptococcosis often presents with cryptococcemia, and is characterized by involving unusual sites such as (eg, the transplant organ or surgical sites[7]). There are many causes for hyperbilirubinemia in the early postoperative period including preservative injury, rejection, reactivation of hepatitis B or C virus infection, or other liver infections, which may need a liver biopsy to differentiate. It is also important to meticulous reading of the liver biopsy smear when the common causes for hyperbilirubinemia do not exist. This is the mainstay for finding a clue for uncommon infection to prevent consequent severe infection and mortality.

Some of these patients may have unrecognized pretransplant or donor-derived disease. By performing the pretransplant serologic screening for *Cryptococcus*, it may give us a better understanding of the recipients. Therefore, it is crucial to obtain a more-thorough history, and information from every donor or relative or even additional serologic screening of high-risk and marginal donors to safely use these organs to overcome organ shortage worldwide.

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