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BRIEF REPORT

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Successful treatment of disseminated cryptococcosis in a liver transplant recipient with fluconazole and flucytosine, an all oral regimen

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Abstract Amphotericin B, with or without 5-flucytosine, is currently the therapy of choice for cryptococcal infections. However, amphotericin B, is nephrotoxic and requires long-term venous access for parenteral administration. The combination of fluconazole and flucytosine is synergistic in vitro against *Cryptococcus*. To date, however, the efficacy of fluconazole and flucytosine for cryptococcosis in liver transplant recipients has never been reported. We report a 66-year-old liver transplant recipient with disseminated invasive cryptococcus (presenting as cryptococcal subcutaneous abscess, osteomyelitis, and serum cryptococcal antigen titer of 1:32). The administration of amphotericin B for 3 weeks led to nephrotoxicity without any clinical response (persistent abscess without change in serum cryptococcal antigen titer). Fluconazole, at a dosage equivalent to 800 mg/day administered orally, and flucytosine, also given orally, led to a clinical response and a steady decline in serum cryptococcal antigen titer, which became negative at 6 weeks of therapy. The patient remains well 18 months after therapy. No adverse effects have been attributed to fluconazole or flucytosine. This combination obviates the nephrotoxicity and the need for parenteral access required for amphotericin B infusion, and it can be administered orally. The combination of fluconazole and flucytosine warrants future controlled trials for the treatment of cryptococcal infection in liver transplant recipients.

Key words *Cryptococcus*, liver transplantation, antifungal therapy · Liver transplantation, *Cryptococcus*, antifungal therapy · Fluconazole, flucytosine, *Cryptococcus*, liver transplantation

Introduction

Cryptococcal infection is a serious, opportunistic fungal infection in immunocompromised hosts. Its incidence ranges between 8% and 10% in HIV-infected patients and between 1% and 5% in organ transplant recipients [3, 4, 5, 10, 15]. Amphotericin B, with or without flucytosine or fluconazole, is currently employed for the treatment of cryptococcosis; however, the usefulness of these regimens is hampered by their frequent side effects and/or their poor therapeutic efficacy. Furthermore, the intravenous formulation of amphotericin B necessitates long-term venous access and may prolong hospitalization. Fluconazole can be administered orally; however, the clinical success rate with its use alone in treating HIV-infected patients with cryptococcal meningitis has only reached 34% [11].

It has been shown that the combination of fluconazole and flucytosine is synergistic against *Cryptococcus neoformans* in vitro [9]. However, the efficacy of this regimen against *Cryptococcus* has never previously been demonstrated clinically in transplant recipients. We report a liver transplant recipient with dis-

seminated cryptococcosis who was treated successfully with an all oral regimen of fluconazole and 5-flucytosine.

Case report

A 66-year-old male underwent orthotopic liver transplantation for end-stage liver disease due to alcohol use. Post-transplant immunosuppression consisted of tacrolimus and prednisone. Six weeks post-transplant the patient experienced primary cytomegalovirus infection without symptomatic disease. Nine months post-transplant the patient presented at another hospital with a 1-month history of increasing fatigue, loss of appetite, weight loss of 20 pounds, a painful, soft tissue mass in the left thigh, and pain in the right lower leg. His medication consisted of tacrolimus, 5 mg p.o., b.i.d.; trimethoprim-sulfamethoxazole, 160/800 mg p.o., every other day; and nifedipine. His white blood cell count was 3100/mm^3 with 45 % granulocytes, and serum creatinine was 2.6 mg/dl. The hepatic allograft was functioning normally and the chest radiograph was unremarkable. Radiographic films and bone scan revealed osteomyelitis of the left fibula. A biopsy of the left thigh mass and fibula revealed *Cryptococcus neoformans* in culture and serum cryptococcal antigen was 1:32. Analysis of cerebrospinal fluid was unremarkable for *Cryptococcus*. The patient received amphotericin B (0.5 mg/kg per day) for 3 weeks (along with flucytosine for 1 week) at the other hospital. A rise in serum creatinine to 3.7 mg/dl led to discontinuation of amphotericin B, and the patient was discharged on fluconazole, 200 mg orally daily. Thigh mass had remained unchanged in size.

Two weeks later, the patient was hospitalized in our institution with progressive weight loss and increase in the size of the left thigh mass. The serum cryptococcal antigen titer was still elevated at 1:32 and serum creatinine was 3.8 mg/dl. Tacrolimus was immediately decreased to 3 mg p.o., b.i.d. and then gradually decreased to 1 mg p.o., once a day, within 30 days of admission. An excisional biopsy of the thigh mass revealed cryptococci histopathologically and in culture. Fluconazole, 400 mg p.o. daily, and flucytosine, 50 mg/kg p.o. daily, were initiated. Serum cryptococcal antigen declined to 1:8 at 2 weeks, to 1:2 at 4 weeks, and then became negative at 6 weeks, at which point flucytosine was discontinued. Fluconazole, 200 mg once daily, was continued for 4 months after the serum cryptococcal antigen became negative. No adverse effects could be attributed to fluconazole or 5-flucytosine. The patient remains well at 24 months of follow-up. His current immunosuppressive regimen consists of tacrolimus, 2 mg p.o., b.i.d., and mycophenolate mofetil, 1 gram p.o., b.i.d.

Discussion

Despite the availability of a number of antifungal agents active against *Cryptococcus*, the treatment of this infection remains challenging. The administration of high-dose amphotericin B frequently results in rapid onset of renal dysfunction, necessitating dosage reduction or discontinuation of therapy. Transplant recipients are particularly susceptible to the nephrotoxicity of amphotericin B since its concomitant use with cyclosporin or tacrolimus can precipitate renal failure. Renal dysfunction in the early post-transplant period, particularly the requirement of dialysis, can be detrimental in liver transplant patients [2, 7, 8, 14]. Data from our institution show a significantly higher mortality in the early post-transplant period in critically ill liver transplant recipients requiring dialysis (54 %) than in those not requiring dialysis (5 %, $P = 0.0005$) [14].

While dosage reduction of amphotericin B may ameliorate renal toxicity, lower dosages of amphotericin B are not very efficacious; a clinical success rate of only 40 % was reported in AIDS patients with cryptococcal meningitis, and a median of 42 days of therapy was required for sterilization of cerebrospinal fluid [11]. The overall efficacy of amphotericin B can be improved when it is combined with flucytosine; however, amphotericin B requires long-term vascular access with its attendant risk of catheter infections and possibly prolonged hospitalization. Fluconazole has a relatively safe toxicity profile and can be administered orally. However, the clinical response rate with fluconazole alone is lower than with amphotericin B, and fluconazole does not render the cerebrospinal fluid culture negative for cryptococci as rapidly as amphotericin B [11].

Combination therapy with fluconazole and flucytosine is an attractive therapeutic option given the feasibility of oral administration of both drugs. In a pilot study in HIV patients with cryptococcal meningitis, the combination was associated with a clinical success rate (sterilization of the cerebrospinal fluid) in 63 % of the patients [6]; the cerebrospinal fluid sterilization rate with amphotericin B alone is approximately 40 % and with fluconazole alone is about 35 % [6]. An in vitro combination of fluconazole and flucytosine against 50 clinical strains of *Cryptococcus neoformans* demonstrated synergy in 62 % of the cases and antagonism in none [9]. In a murine model of cryptococcal meningitis, combined therapy with fluconazole and flucytosine significantly prolonged survival when compared with controls and with groups receiving fluconazole or flucytosine alone [1]. Quantitative cultures revealed significantly lower cryptococcal fungal load in the brain tissue of mice receiving the combination therapy [1].

Based on these data we employed fluconazole and 5-flucytosine as therapy for our patient. Abnormal renal function precluded continued use of high-dose amphotericin B in our patient. Although liposomal preparations of amphotericin B appear effective and are less nephrotoxic [13], the expense and requirement of parenteral access are potential drawbacks. Elevation of serum creatinine (due to an increase in cyclosporin or tacrolimus levels) can also be observed with fluconazole in transplant recipients. However, with careful monitoring of cyclosporin and tacrolimus levels, this adverse effect can be obviated. A deterioration in renal function was not observed in our patient despite his having received the equivalent of 800 mg of fluconazole daily. A reduction in immunosuppression and debulking of the

cryptococcal thigh mass most likely contributed to a successful outcome in our case. The patient remains well at 24 months of follow-up.

We believe that flucytosine is a critical component of the antifungal regimen for the treatment of acute cryptococcal infection. In a recently completed study comparing fluconazole with itraconazole as maintenance therapy to prevent relapse of cryptococcal meningitis in HIV patients, the lack of use of flucytosine as induction therapy was the most significant predictor of relapse [12]. Flucytosine at currently recommended dosages of 150 mg/kg per day can be associated with serious marrow toxicity. A noteworthy feature of the fluconazole plus flucytosine combination is that the addition of fluconazole greatly reduced the flucytosine minimum inhibitory concentration for the cryptococcal isolates, even for the strains that did not demonstrate frank synergy [9]. Thus, an additional advantage of the combination therapy is the reduction in the amount of flucytosine required and, therefore, the potential to reduce dose-related toxicity. Our patient received 25 mg/kg of flucytosine b.i.d., with serum levels ranging from a trough of 30 μg/ml to a peak of 94 μg/ml. No adverse effect could be attributed to flucytosine or fluconazole.

In summary, our case demonstrates the efficacy of fluconazole plus flucytosine for the treatment of disseminated cryptococcosis after liver transplantation. The combination of fluconazole plus flucytosine may enhance the efficacy of the former and reduce the toxicity of the latter. More importantly, this all oral regimen has the potential advantage of being used to treat less seriously ill patients as outpatients. Given our success in this anecdotal case of disseminated invasive cyptococcal infection, this combination warrants study in future controlled trials for the treatment of cryptococcal infections in transplant recipients.

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