CASE REPORT

Cryptococcal Hepatic Infection Mistaken for Fluconazole-Induced Hepatotoxicity

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Fluconazole is a new triazole antifungal agent with novel pharmacologic and pharmaceutical properties. These properties include a high level of activity against *Cryptococcus* and *Candida* species; good bioavailability after oral administration; and excellent distribution into the cerebrospinal fluid (CSF).

Fluconazole is now accepted as standard maintenance therapy for patients who have acquired immunodeficiency syndrome (AIDS) with cryptococcal meningitis, once they have completed an initial course of amphotericin B (usually 1 g).[1] However, its role as initial therapy for cryptococcal meningitis is still being evaluated. One large, randomized study comparing fluconazole (200 to 400 mg/day) with amphotericin B either alone (0.3 to 0.7 mg/kg/day) or with flucytosine for the treatment of cryptococcal meningitis in AIDS patients found that the microbial success of the agents was comparable, but low (34% for fluconazole; 40% for amphotericin B).[2] The low cure rate suggested that both regimens may have been suboptimal. Another trial by Larson et al has also suggested that fluconazole (200 mg/day) is suboptimal as an initial treatment for cryptococcal meningitis in AIDS patients.[3] Several recent studies have suggested that the microbial and clinical success rates could be greatly improved with higher initial doses of fluconazole (400 to 800 mg/day).[4,5] One study reported that six patients with cryptococcal meningitis were cured of infection with an initial IV fluconazole dose of 1600 mg followed by additional doses of 800 mg/day until eight weeks after the patients' CSF cultures tested negative for infection.[4]

Several randomized controlled trials have shown fluconazole to be an effective treatment for mucosal candidiasis, including esophagitis.[6,7] One recent report documents that for patients without neutropenia or major immunodeficiency, fluconazole and amphotericin B are not significantly different in their effectiveness in treating candidemia.[8]

Fluconazole has been relatively well tolerated. Adverse effects observed in clinical trials were nausea, skin rash, and aminotransferase elevations. However, published case reports have documented instances of acute hepatic necrosis during fluconazole treatment.[1,9,10] The reports of fluconazole-induced hepatic necrosis could cause the clinician to suspect that all signs of hepatic pathology in patients receiving fluconazole are the result of fluconazole administration. Such suspicions could result in premature reduction of dosage or inappropriate discontinuation of fluconazole therapy.

We describe a patient with AIDS who developed elevations in liver function test levels after receiving fluconazole for cryptococcal meningitis. We suspected the presence of fluconazole-induced hepatotoxicity, but a needle biopsy of the liver demonstrated cryptococcal hepatic infection.

CASE

A 25 year-old woman weighing 45 kg came to the clinic with a one-month history of sore throat, fever, chills, night sweats, and severe headaches with visual complaints. She had been well until one year before the visit, when she had begun to develop sinus congestion, fullness in the ears, a nonproductive cough, and mild shortness of breath. Her past medical history included a tubal ligation and two episodes of genital herpes. Her husband had previously tested positive for the human immunodeficiency virus (HIV). The patient was taking no medications. She was admitted to the hospital.

At the time of admission, the patient's vital signs were as follows: temperature, 39.1°C; blood pressure, 130/94 mmHg; heart rate, 96 per min; respirations, 18 per min. Physical examination revealed bitemporal wasting, white plaques on the hard palates, and no lymphadenopathy. The patient complained of "fullness" in

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her eyes but was experiencing no diplopia. Her lungs were clear to auscultation. A neurological evaluation revealed that she was awake, alert, and oriented as to time, place, and person. Cranial nerves II through XII were intact, strength was intact, and there was no Babinski reflex. Proprioception was intact bilaterally and there were no meaningeal signs.

Results of admission laboratory studies included a hematocrit level of 31.6 and a white blood cell count of 2.2 $X10^3$ cells/mm^3 with 53% neutrophils, 11% band cells, 30% lymphocytes, 5% mononuclear cells, and 1% eosinophils. Her platelet count was 95,000/mm^3, and her CD_4 cell count was 10 cells/mm^3. Other serum levels were as follows: urea 5 mmol/L; serum creatinine 53 mmol/L; glucose 4.8 mmol/L; calcium 1.1 mmol/L; phosphate 1.8 mmol/L; total protein 75 g/L; and albumin 33 g/L. The results of liver function tests performed at the time of admission are found in Table I. The results of serology tests were positive for HIV and the hepatitis B core antibody but negative for hepatitis B surface antigen, rapid plasma reagin, and hepatitis C antibody. A CT scan of the head revealed no lesions. The results of a lumbar puncture revealed the following CSF levels: glucose 1.2 mmol/L; protein 120 g/L; and no red cells and 1 white cell per high-power field. Gram straining revealed no organisms, but the CSF was positive for cryptococcal antigen. Blood cultures were positive in 3 of 3 bottles for *Cryptococcus neoformans*. Serum cryptococcal titer was positive at a dilution of 1:2.

A diagnosis of cryptococcal meningitis was made and treatment was begun with fluconazole (400 mg IV daily). A test dose of amphotericin B was given and later increased to 30 mg/day IV. The patient was also placed on cotrimoxazole DS (one tablet p.o. daily) and zidovudine (100 mg p.o. tid). Because the patient's hepatic enzyme levels were abnormal and increasing (Table I), on day five dosage of fluconazole was reduced to 200 mg p.o. daily. In addition, cimetidine (300 mgq8h) was begun for stomach upset and megestrol (80 mg p.o. qid) was added for appetite stimulation.

On the tenth day, fluconazole-induced hepatotoxicity was suspected but abdominal ultrasound revealed no abnormalities. On day 11, acyclovir (200 mg p.o. five times per day) was started for the treatment of genital herpes simplex. By day 19, the patient was afebrile and clinically improved except for occasional headaches. However, because her hepatic enzyme levels remained elevated, a liver needle biopsy was performed, fluconazole treatment was discontinued, and treatment with itraconazole (200 mg p.o. bid) was started. Results of the needle biopsy showed a non-necrotizing granulomatous lesion with fungal organisms consistent with *Cryptococcus neoformans*. Fluconazole treatment (400 mg p.o. daily) was restarted two days later and the itraconazole was discontinued.

The patient was discharged from the hospital on day 25. Medications continued at home included amphotericin B (30 mg IV daily to a total of 1), zidovudine (100 mg p.o. tid), acyclovir (200 mg p.o. five times daily), cotrimoxazole DS(one tablet p.o. daily), amitriptyline (25 mg p.o. for sleep), and fluconazole (200 mg p.o. daily). Six months after discharge, the patient continues to do well without relapse and liver enzyme levels remain normal or nearly normal.

DISCUSSION

Cryptococcus neoformans is the most common cause of systemic mycoses in patients with AIDS, occurring in up to 10% of patients.[11-13] It presents most commonly as meningitis or pneumonitis and in immunocompromised hosts it is often widely disseminated.[11-13] Extraneural sites of infection are less common in patients with AIDS and fungemia is present in as many as 80% of AIDS patients with cryptococcal meningitis. The initial treatment for these patients is usually amphotericin B to a cumulative dose of at least 1 g. Maintenance therapy continues for life with either fluconazole (200 mg/day) or amphotericin B. This patient's attending physician began initial treat-

Table I: Liver Function Tests

	Hospital Day									
	1	3	4	5	6	7	10	14	17	54 days after hospitalization
AST (13-35 U/L)*	52	57	65	56	67	42	69	40	19	25
ALT (7-35 U/L)	29	31	33	30	34	27	68	53	25	13
LDH (100-190 U/L)	246	236	370	294	344	230	247	370	244	274
AP (30-100 U/L)	344	363	462	517	478	440	649	542	347	90
GGT (10-50 U/L)	179	163	204	221	215	212	402	497	397	68
Total bilirubin (3.4 - 18.8 mmol/L)	8.6	5.1	10.3	5.1	5.1	5.1	10.3	17.1	13.7	10.3

*All values in parentheses are laboratory normal values.
AST = aspartate aminotransferase (SGOT)
ALT = alanine aminotranferase (SGPT)
LDH = lactate dehydrogenase
AP = alkaline phosphatase
GGT = gamma-glutamyltransferase

ment with fluconazole (400 mg/day) before the definitive diagnosis was made. After the diagnosis of cryptococcal meningitis had been confirmed, amphotericin B was added to the treatment regime. The original plan had been to stop the fluconazole treatment once the patient had started amphotericin B; however, because of the severity of the patient's clinical condition and her persistent headaches, the plan was altered to include both drugs.

The involvement of the liver in this patient's systemic cryptococcal infection parallels the presentation of hepatosplenic candidiasis, in which the diagnosis is often delayed as a result of a non-specific clinical syndrome. The normal presentation of hepatosplenic candidiasis is fever with upper right quadrant pain, non-diagnostic results of abdominal ultrasound, and blood cultures without growth of a pathogen.[14] Diagnosis of hepatosplenic candidiasis is made by the histopathology seen in a liver biopsy specimen. Our patient's liver involvement went unrecognized until we had received the results of the liver biopsy. Although her admission blood cultures were positive for *Cryptococcus neoformans*, the results of an abdominal ultrasound examination were within normal limits.

Our patient's increasing liver function enzyme levels raised a serious concern that she had fluconazole-induced liver damage. Because of this concern, fluconazole was discontinued and itraconazole was initiated. Jacobson et al[10] described a case of fatal acute hepatic necrosis in a 32 year-old man with AIDS who was receiving fluconazole (400 mg p.o. daily) for cyptococcal meningitis. After 18 days of fluconazole therapy, Jacobson's patient experienced a dramatic elevation in hepatic enzyme and bilirubin levels. AST levels increased from 34 U/L to 2,770 U/L, and ALT levels increased from 70 U/L to 1,825 U/L. The histopathology was more consistent with massive hepatic necrosis than with autolysis, because islands of hepatocytes were spared. In contrast, our patient's increases in aminotransferase enzyme levels were less pronounced. However, her alkaline phosphatase level increased to 649 U/L, whereas the alkaline phosphatase levels of Jacobson's patient were no higher than 222 U/L.

Munoz et al reported three cases of fluconazole-induced hepatotoxicity.[9] All cases were characterized by transaminase elevations after the administration of fluconazole in oral doses of 50 mg daily for 14 days for the treatment of esophageal candidiasis in AIDS patients. In two of the cases the hepatic enzyme levels returned to normal when fluconazole was withdrawn. In the third case, the patient became icteric by the tenth day of treatment and died five days later.

In clinical trials in which fluconazole therapy lasted longer than seven days, 16% of patients experienced adverse effects.[7] Approximately 1% of patients experienced transaminase elevations of more than eight times the normal upper limit during the trials. According to the manufacturer of the drug, these elevations tended to occur in patients with severe underlying diseases, such as AIDS or malignancy, who were being treated with multiple medications, including those known to be hepatotoxic.[7]

Because fluconazole has the potential to induce hepatic injury, it is prudent to obtain baseline hepatic function levels before treatment begins and periodically during therapy. This is particularly true for patients with serious infections who will receive high doses for a long period of time. It is not known whether hepatotoxicity is dose-related because toxicity has been reported in both high- and low-dose regimens. Our experience underscores the importance of considering other causes of hepatotoxicity when fluconazole therapy is given to an immunocompromised patient.

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