Hepatosplenic Candidiasis: Successful Treatment with Fluconazole

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PURPOSE: To determine if fluconazole is effective treatment for hepatosplenic candidiasis that has not resolved with amphotericin B and fluconazole treatment.

PATIENTS AND METHODS: Six patients (ages 3 to 44) with acute leukemia and hepatosplenic candidiasis who did not respond to prior antifungal therapy were treated with fluconazole.

RESULTS: All six patients had fever and three had nausea and vomiting; computed tomographic (CT) scan showed lucencies in the liver in six, lucencies in the spleen in five, and lucencies in the kidneys in three. Prior therapy with 1.6 to 4 g of amphotericin B in the five adults and 526 mg of amphotericin B in the child (with the addition of flucytosine in four) failed to improve clinical symptoms or lucencies in the liver, spleen, and kidneys seen on CT scan. Fluconazole was given at a dose of 200 to 400 mg daily (70 to 100 mg in the child) for 2 to 14 months. All patients had resolution of fever and other symptoms in 2 to 8 weeks. Improvement of the lesions noted on CT scan was seen in 4 to 8 weeks in all patients. Total resolution of lesions noted on CT scan occurred by 4 weeks in two patients, but took 4 to 5 months for three patients and 13 months for one patient. Three patients had relapse of their acute leukemia and two died, presumably cured of their candidiasis. Two patients underwent successful bone marrow transplantation without relapse of their candidiasis.

CONCLUSION: Fluconazole appears to be useful in the treatment of hepatosplenic candidiasis that has not resolved with amphotericin B and fluconazole treatment.

August 1991 The American Journal of Medicine Volume 91 137
TABLE I
Clinical Characteristics and Response to Prior Antifungal Therapy

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age/Sex</th>
<th>Sites</th>
<th>CT Scan</th>
<th>Pathology</th>
<th>Culture</th>
<th>Prior Treatment (duration)</th>
<th>AmB*</th>
<th>5-FC</th>
<th>Keto</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32/M</td>
<td>LS</td>
<td>LS (+)</td>
<td>L (+)</td>
<td>L (+)</td>
<td>1.5 months (1.6 g)</td>
<td>—</td>
<td>—</td>
<td>2 weeks</td>
</tr>
<tr>
<td>2</td>
<td>44/F</td>
<td>L,K</td>
<td>L,K (+)</td>
<td>L (+)</td>
<td>L (-)</td>
<td>6 months (2.9 g)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>36/F</td>
<td>L,S,K</td>
<td>L,S,K (+)</td>
<td>L (+)</td>
<td>L (-)</td>
<td>3 months (3.5 g)</td>
<td>2 months</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3/F</td>
<td>L,S,K</td>
<td>L,S,K (+)</td>
<td>L (+)</td>
<td>L (+)</td>
<td>3 months (4 g)</td>
<td>3 months</td>
<td>1 month</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>44/M</td>
<td>L,S</td>
<td>L,S (+)</td>
<td>L (+)</td>
<td>L (-)</td>
<td>2.5 months (2.9 g)</td>
<td>2.5 months</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>18/M</td>
<td>L</td>
<td>L,S (+)</td>
<td>S (+)</td>
<td>S (-)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

AmB = amphotericin B; 5-FC = flucytosine; Keto = ketoconazole; L = liver; S = spleen; K = kidneys.

* Number in parentheses = total dose of amphotericin B.

TABLE II
Response to Fluconazole Treatment

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Fluconazole Therapy</th>
<th>Response to Therapy</th>
<th>Clinical</th>
<th>CT Scan</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200 (mg) 2 weeks</td>
<td>Fever resolved—Week 3; nausea, vomiting worse, fever returned (due to leukemia)</td>
<td>Normal—Week 4</td>
<td>—</td>
<td>Candidiasis resolving; leukemia relapsed and patient died</td>
</tr>
<tr>
<td></td>
<td>400* (mg) 1.5 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>200 (mg) 2 weeks</td>
<td>Fever resolved—Week 4; nausea, vomiting resolved—Week 6</td>
<td>Normal—Week 4</td>
<td>—</td>
<td>Candidiasis resolved; BM Tx in 5 months after therapy stopped—no relapse of candidiasis</td>
</tr>
<tr>
<td></td>
<td>400* (mg) 1.5 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>200 (mg) 2 weeks</td>
<td>Fever resolved—Week 6; nausea, vomiting resolved—Week 8</td>
<td>Normal—Week 4</td>
<td>—</td>
<td>Candidiasis resolved; leukemia relapsed and patient died</td>
</tr>
<tr>
<td></td>
<td>400 (mg) 5.5 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>70* (mg) 3 months</td>
<td>Fever resolved—Week 8</td>
<td>Normal—Week 4</td>
<td>—</td>
<td>Candidiasis resolved; leukemia in remission</td>
</tr>
<tr>
<td></td>
<td>100 (mg) 11 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>200 (mg) 6 weeks</td>
<td>Fever resolved—Week 4</td>
<td>Normal—Week 4</td>
<td>—</td>
<td>Candidiasis resolved; leukemia relapsed after fluconazole stopped</td>
</tr>
<tr>
<td></td>
<td>400 (mg) 11 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>200 (mg) 2 weeks</td>
<td>Fever intermittent prior to fluconazole, felt better by Week 2</td>
<td>Normal—Week 4</td>
<td>—</td>
<td>Candidiasis resolved; BM Tx in Week 10 of therapy—no relapse of candidiasis</td>
</tr>
<tr>
<td></td>
<td>400 (mg) 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

L = liver; K = kidneys; BM Tx = bone marrow transplantation.

* Intravenous fluconazole was given at the dose indicated for 10 days (Patient 1), 8 days (Patient 2), and 3 months (Patient 4).

The sites of involvement were liver (six), spleen (five), and kidneys (three) (Table I).

Diagnostic Studies

Four of the six patients had the diagnosis established by liver biopsy, which showed abscesses with yeast and hyphal forms characteristic of Candida, and one patient had a splenectomy, which revealed multiple abscesses with Candida. Only two of the five tissue specimens yielded Candida albicans when cultured. The sixth patient had a percutaneous liver biopsy, which did not show fungi, but she had already received 2 months of amphotericin B therapy. However, she previously had Candida tropicalis grown from blood and skin lesions 3 months prior to the liver biopsy, characteristic lucencies in the liver and kidney on a CT scan of the abdomen, and persistent fever, nausea, and vomiting. None of the other patients had documented candidemia at any point during their treatment for acute leukemia.

CT scans of the abdomen showed characteristic multiple lucencies in the liver in all patients, with involvement of spleen and kidneys noted less frequently (Table I). At the time of diagnosis of hepatosplenic candidiasis, white blood cell counts varied widely (1,800/μL to 35,000/μL), but were low only in the 3-year-old girl. The alkaline phosphatase level was abnormal in all but one patient (114 U/L to 701 U/L). The bilirubin level was elevated in only one patient, and the alanine aminotransferase and aspartate aminotransferase values were within normal limits in all six.

Prior Antifungal Therapy

All six patients had been treated with amphotericin B as for as long as 1.5 to 6 months, and four received flucytosine concomitantly (Table I). The to-
tal dose of amphotericin B received by the five adults was 1.6 to 4 g (mean = 2.9 g), and the 3-year-old patient received a total of 44 mg/kg. Two patients received ketoconazole, one for 2 weeks and one for 4 weeks.

Fever persisted in all the patients throughout their course of amphotericin B therapy; Patient 6 had only intermittent low-grade fevers, but the other five patients had daily spiking elevations of temperature. Five patients had persistently elevated alkaline phosphatase values. CT scanning showed persistence of lucencies in the liver in two patients and increased number and size of lesions in four patients. Laparotomy after 4 months of therapy with amphotericin B/flucytosine and then ketoconazole in Patient 5 showed multiple liver abscesses with fungi noted on histopathologic examination.

Response to Fluconazole Therapy

All six patients responded to treatment with fluconazole (Table II). Symptoms of fever, nausea and vomiting, and abdominal pain resolved within 3 to 8 weeks. Patient 1 had initial resolution of fever, then recurrence in the fourth week, but this was most likely due to a relapse of his acute leukemia, which progressed to cause his death in Week 9 of therapy.

The level of alkaline phosphatase was not useful in all patients as a measure of response to therapy. In two patients, decreasing alkaline phosphatase values correlated with clinical and CT scan improvement. However, in two others the values fell to normal, only to increase again, probably related to a relapse of leukemia. The child had persistently elevated levels, presumably due to bone growth.

The timing of repeated CT scans was decided by the patient's primary physician so that the actual time of resolution of lesions was not established in most patients. In two patients, the CT scan was normal by Week 4 of therapy; in four patients, improvement in the lesions in the liver was noted by Weeks 5 to 8 of therapy (Figure 1). Two of these four patients showed complete resolution of lucencies on CT scan after 5 months of therapy. The response of Patient 5 was difficult to evaluate because scans were done so infrequently; 13 months after fluconazole treatment was begun, his CT scan was normal. Patient 2 had resolution of lesions in the liver by Week 8, but worsening kidney lesions during this time, with final resolution by Week 14.

Three patients had relapse of their acute leukemia. Patient 1 died of leukemia, and his candidiasis appeared to be resolved but no necropsy was performed. Patient 3 tolerated reinduction chemotherapy, had resolution of candidiasis, but then had another relapse of leukemia and died. Patient 5 had gradual resolution of his candidiasis (by Week 8, symptoms resolved and a CT scan improved, with a normal CT scan documented by Month 13 of therapy with fluconazole), and then had a relapse of leukemia after fluconazole administration had been stopped.

Two patients underwent successful bone marrow transplantation without relapse of their candidia-
sis—one in Month 3 of therapy and one 5 months after therapy had been stopped. Patient 4 had resolution of her candidiasis during maintenance chemotherapy and has done well with no relapse of her leukemia.

The length of therapy was determined by several factors, including the clinical response to therapy, the status of the leukemia, and patient decisions. For example, the two patients who received less than 3 months of therapy did so because one had relapse of leukemia, was not treated with a further course of chemotherapy, and died soon after (Patient 1), and the other patient elected to stop therapy because she believed that fluconazole had caused her to have a seizure (Patient 2). Other patients were treated until both clinical and CT scan resolution had occurred, and were treated for over a year because they were doing well and their physicians believed it best to continue therapy to be certain of cure of their infection.

No side effects of fluconazole therapy were noted. It was not believed that the seizure experienced by Patient 2 was related to fluconazole, especially since a lesion was noted on magnetic resonance imaging scan in an area corresponding to her focal seizure activity.

**COMMENTS**

Hepatosplenic candidiasis has become a major problem in the population of patients with acute leukemia who have undergone successful induction chemotherapy and whose disease is in remission. The development of abdominal complaints and fever may herald the development of this syndrome [3-5]. CT scan or ultrasound examination will usually show the characteristic lesions in liver, spleen, and kidneys [6], and biopsy will show yeast and hyphal forms characteristic of *Candida* in areas with varying amounts of necrosis and granulomatous inflammation. Interestingly, cultures taken from involved tissues are often negative [5]. Despite negative cultures, symptoms persist and the patient will not improve without antifungal therapy. Given the fact that many of these patients will require further markedly immunosuppressive procedures, such as bone marrow transplantation, to definitively treat their leukemia, eradication of visceral foci of *Candida* is essential.

An as yet unexplained aspect of this syndrome is the poor response to therapy with antifungal drugs [4,5,7,8]. The five adults described in this report had received from 1.6 g to 4.0 g of amphotericin B with minimal clinical or radiographic improvement. It is possible, however, that higher daily doses or a longer course of therapy with amphotericin B might have led to resolution of infection in these patients.
when amphotericin B was not is not clear. It is possible that prior therapy with amphotericin B was essential to resolution of hepatosplenic candidiasis in these patients. Perhaps persistence of amphotericin B in the liver well after therapy was stopped contributed to the eventual resolution of infection [14]. Whether fluconazole should be used as primary therapy for this disease has not been answered by this study and would require a multicenter randomized trial comparing amphotericin B with fluconazole.

ACKNOWLEDGMENT

Pfizer-Roerig generously supplied fluconazole for the patients reported herein. We thank Drs. Jeffrey Band and Duane Harrison for providing data on their patients.

REFERENCES