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Refractory Candidal Meningitis in an Immunocompromised Patient Cured by Caspofungin

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Candidal meningitis is a rare infectious disease that usually leads to substantial morbidity and mortality. We present a case of candidal meningitis refractory to systemic antifungal therapy (amphotericin B and fluconazole). A 63-year-old female with lymphoblastic lymphoma and myelodysplasia with leukemia transformation developed prolonged fever and headache on the seventh day following intrathecal prophylactic chemotherapy. A lumbar puncture showed neutrophilic pleocytosis, and a cerebrospinal fluid culture yielded *Candida albicans*. The clinical course was complicated by brain edema, subarachnoid hemorrhage, and hydrocephalus. Parenteral therapy with amphotericin B alone or amphotericin B in combination with fluconazole or intrathecal administration of amphotericin B failed to eradicate *C. albicans* in the cerebrospinal fluid. After 7 days of caspofungin therapy, however, the cerebrospinal fluid became sterile and the patient gradually regained consciousness. She was discharged 1 month after completing 4 weeks of caspofungin therapy. There were two critical issues we thought to be relevant to the favorable outcome of this case. First, isolation of *C. albicans* was achieved by inoculating enriched liquid medium with cerebrospinal fluid. Second, there is a potential therapeutic benefit of caspofungin in treating a fungal infection of the central nervous system.

CASE REPORT

A 63-year-old woman had lymphoblastic lymphoma and myelodysplasia with leukemia transformation, initially presenting as a neck mass, anemia, and thrombocytopenia. She received the first course of chemotherapy, consisting of a hyperCVAD regimen (cyclophosphamide, vincristine, epirubicin, and dexamethasone), on 23 December 2002 and the second course of chemotherapy on 14 February 2003 (day 1). The latter treatment included intrathecal methotrexate (day 2) and intrathecal cytosine arabinoside (day 8). Neutropenic fever developed 8 days after initiation of chemotherapy, accompanied by progressive headache and vomiting. The fever did not subside under parenteral treatment with vancomycin and meropenem. A lumbar puncture was therefore done on day 23, and study of the cerebrospinal fluid (CSF) revealed neutrophilic pleocytosis (white blood cell count, 1,500/mm^3; 87% neutrophils). The patient's consciousness deteriorated following the lumbar puncture, a phenomenon thought to be related to a subarachnoid hemorrhage and brain edema (Fig. 1A). The patient was treated for bacterial meningitis on the basis of the initial CSF data. An Omaya reservoir was inserted on day 27 because of hydrocephalus. CSF drawn from the Omaya reservoir on day 33 yielded *Candida albicans*. Amphotericin B (1 mg/kg of body weight per day) was given for central nervous system (CNS) candidiasis, starting on day 39. Brain magnetic resonance imaging (MRI) scans on day 41 showed hydrocephalus and hematoma over the premedullary space, which was thought to be the result of a rupture of a mycotic aneurysm (Fig. 1B). However, after 29 days of amphotericin B therapy, with a cumulative dose of 1.45 g, the patient's CSF still yielded *C. albicans*. Intravenous fluconazole (400 mg/day) was added on day 74. *C. albicans* was not eradicated by combination therapy and installation of a new Omaya reservoir on day 78. Intrathecal amphotericin B therapy (1 ml, 0.25 mg/ml, three times a week) was started on day 85. The MICs of amphotericin B and fluconazole, determined by Etest (AB BIODISK, Solna, Sweden) on RPMI 1640 agar containing 2% glucose, for the *C. albicans* CSF isolates obtained increased during the treatment course (Table 1).

Because of the apparent microbiological failure of parenteral (accumulative dose, 3.1 g) and intrathecal (total, seven doses) amphotericin B in combination with fluconazole over a period of 24 days, caspofungin (70 mg on the first day, i.e., day 103, followed by 50 mg/day) was administered parenterally after informed consent was obtained from the patient's family. The CSF became sterile after 7 days of caspofungin use, as shown in Table 2. A ventriculoperitoneal shunt was inserted to replace the Omaya reservoir after 25 days of caspofungin use. The peak and trough levels of caspofungin, measured by high-performance liquid chromatography with fluorescence detection, were 4.2 and 2.5 g/dl after administration of the first dose of caspofungin and 8.0 and 3.7 g/dl after 24 days of therapy. Caspofungin was given for a total of 28 days, followed by maintenance therapy with 400 mg of oral fluconazole per day. The patient regained consciousness after installation of the ventriculoperitoneal shunt. Follow-up MRI brain scans dem-

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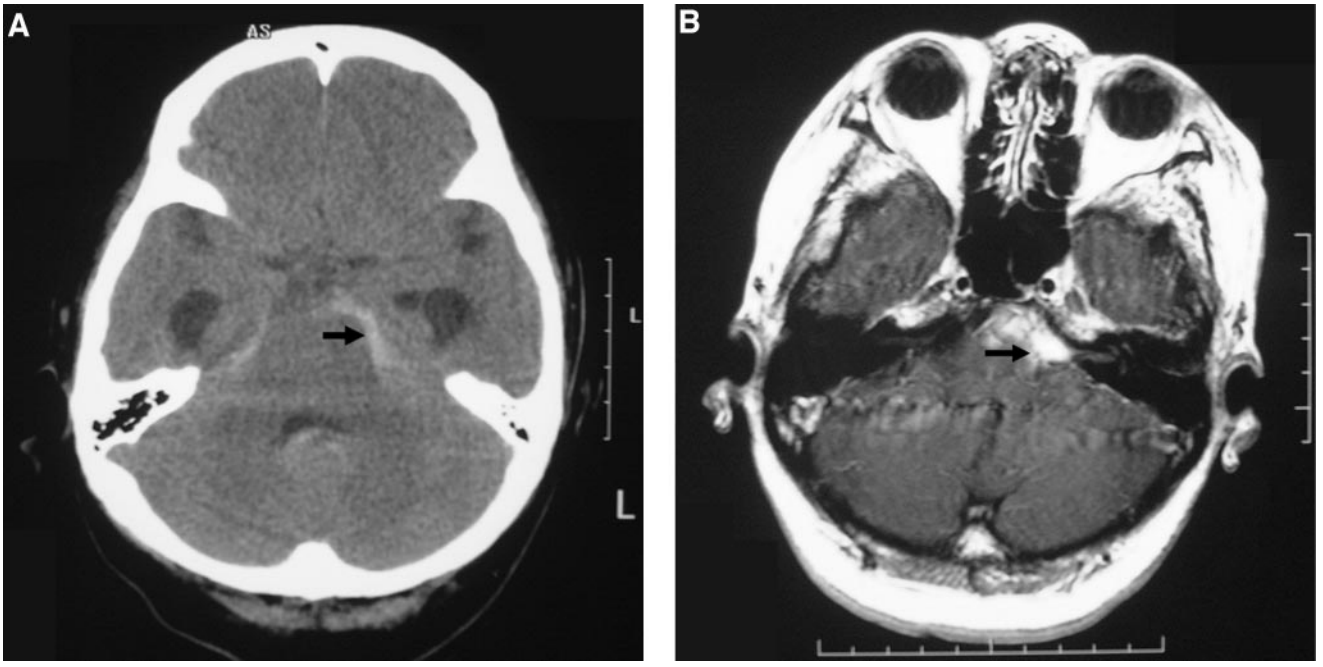

FIG. 1. Candidal meningitis in a case with hematological malignancy. (A) Computed tomography of the brain with contrast medium on day 24 showing a subarachnoid hemorrhage over the posterior fossa, especially the left cerebropontine angle (arrowhead). (B) MRI scan of the brain on day 41 demonstrating a hematoma (arrowhead) over the premedullary space.

onstrated resolution of the previously observed hematoma. The patient was discharged 1 month after completion of caspofungin therapy.

Discussion. Invasive candidal infections have been increasing in incidence over the past decade. This is the result of an expanding population of immunosuppressed patients, such as those with hematological malignancy and transplants, and the widespread use of broad-spectrum antibiotics, intravenous catheters, and parenteral nutrition (13). Although rare, *Candida* spp. can infect both the meninges and parenchymal brain tissue. The clinical manifestations of CNS candidiasis are varied and include meningitis, scattered brain microabscesses, ventriculitis, vascular complications, and cerebral macroabscesses (13). The morbidity and mortality rates associated with candidal meningitis are substantially high, especially in adults (5, 14). Although amphotericin B—with or without flucytosine—has been recommended as the treatment of choice for candidal meningitis in many studies and case reports (6, 10, 13), an optimal therapeutic regimen has not been established. Although fluconazole has been reported to be effective in treating CNS candidiasis, there have also been several reports of therapeutic failures (1, 9, 13). We have presented a case of candidal meningitis refractory to conventional antifungal therapy (amphotericin B and/or fluconazole). Caspofungin therapy resulted in a favorable outcome.

TABLE 1. MICs of amphotericin B and fluconazole for three *C. albicans* isolates from the CSF of a patient with candidal meningitis refractory to conventional antifungal therapy

Drugs	MIC (μg/ml)		
	Day 33	Day 71	Day 91
Amphotericin B	0.094	0.38	0.5
Fluconazole	0.094	0.094	0.125

Candidal meningitis is a rare and serious disease that may result in significant morbidity and mortality if not recognized and treated effectively (2). In adults, it is seen most commonly in neurosurgical patients, immunocompromised patients, and patients with disseminated candidiasis (6, 13). Although direct inoculation into the CNS and hematogenous spread have been postulated as the mechanisms accounting for candidal meningitis (6, 13, 14), the exact pathogenesis remains unknown. The clinical manifestations of candidal meningitis are variable, including altered consciousness, fever, meningismus, and focal neurological deficits (6, 13). Unfortunately, these symptoms are usually nonspecific and indolent. Subarachnoid and intracerebral hemorrhages have been recognized as complications of candidal meningitis (11), as seen in our patient. The diagnosis relies mainly on CSF culture, but laboratory values are not consistently helpful (5, 6, 13). In fact, there is substantial variability in CSF analysis. Several confounding factors complicate the establishment of a clinical diagnosis of candidal meningitis. First, it is difficult to isolate *Candida* species from CSF because of the small inoculum size and slow growth. Second, isolated microorganisms must be ruled out as a source of contaminants. Third, the CSF cytological and biochemistry profile is too variable to allow a differential diagnosis. Despite the above diagnostic obstacles, there are several methods for improving the success of CSF isolation, such as culturing a large volume of CSF (a minimum of 5 ml), ventricular CSF, and sediment of CSF centrifugation; use of a submicron filter; and inoculating CSF into enriched liquid medium (13, 14), as

TABLE 2. Sequential profiles of CSF from a compromised individual with *C. albicans* meningitis

Day[a]	Amphotericin B dose (g)[b]	Days of caspofungin use	CSF culture for *C. albicans*[c]	No. of RBC/mm^3 of CSF[e]	No. of WBC/mm^3 of CSF[f]	% S/M/L[d]	CSF glucose level (mg/dl)	CSF protein level (mg/dl)
23	0		−	110,000	1,500	87/6/7	18	686
33	0		+	5,616	576	84/0/16	83	106
40	0		+	72	1,158	81/19/0	59	117
43	0.05		+	58	145	72/21/7	74	78
57	0.75		−	120	10	10/70/20	57	49
65	1.15		−	2,080	20	65/30/5	65	109
71	1.40		+	8	13	70/15/15	63	36
78	1.80		+	57	24	66/34/0	74	30
103	2.90	1	+					
104	2.95	2	+	11	14	70/12/18		75
107	3.10	5						
109		7	−	3,890	13	61/19/18	41	42
116		14	−	0	35	72/8/20	45	50
126		24	−	0	4	0/25/75	54	33

[a] Day 0, the day chemotherapy was started; day 23, the first day a lumbar puncture was performed.
[b] Cumulative dose of parenteral amphotericin B. Total cumulative dose, 3.1 g.
[c] + and −, positive and negative for growth of *C. albicans* in CSF.
[d] Percentages of segmented neutrophils (S), monocytes (M), and lymphocytes (L), respectively.
[e] RBC, red blood cells.
[f] WBC, white blood cells.

done in our case. Imaging studies, including computed tomography and MRI scans were of little help in arriving at a definite diagnosis. In fact, the pathogen was not discovered in fungal semisolid culture medium until a special blood culture medium, MYCO/F-Lytic of the BATEC 9240 automated blood culture system (Becton Dickinson Microbiology, Sparks, Md.), was used.

The most appropriate treatment for candidal meningitis has not been established, although previous studies have recommended systemic administration of amphotericin B, with or without flucytosine, as the treatment of choice for candidal meningitis (6, 10, 13). Although intrathecal administration of amphotericin B has been suggested, there are some possible toxic effects on the CNS, such as acute encephalopathy or myeloradiculitis (13). Often such an approach is reserved for patients in critical condition or for those who have proven intolerant of systemic amphotericin B. As fluconazole has excellent CSF penetration and is highly active against most *Candida* spp., it should be theoretically effective against candidal meningitis. However, numerous therapeutic failures with this approach have been reported (1, 9, 13). Data from an animal study also suggested that amphotericin B sterilizes the CSF faster than fluconazole does (8). Thus, the role of fluconazole remains controversial.

Caspofungin, one of the echinocandins, is a semisynthetic, water-soluble, amphipathic lipopeptide that blocks the synthesis of β(1,3)-D-glucan in the fungal cell wall via noncompetitive inhibition of β(1,3)-D-glucan synthase (4). The U.S. Food and Drug Administration has approved it for treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole), as well as for treatment of oropharyngeal and esophageal candidiasis and invasive candidiasis in adults (4). Because of its high molecular weight, high level of protein binding, and hydrophilic properties, in the absence of inflammation, caspofungin has shown poor penetration of the brain or CSF (4). However, in a murine model, a comparison of candidal loads in brain tissues showed that caspofungin alone reduced candidal invasion of the brain (7). In clinical trials, a few patients with CNS aspergillosis also appeared to respond to caspofungin therapy (3, 4). Moreover, candidiasis associated with biofilm formation on bioprosthetic devices, such as an intravenous line or a central nervous system shunt, is problematic because candidal organisms in the biofilm have reduced susceptibility to antifungal drugs. Removal of the affected device is often needed. Previous study indicated that caspofungin was more effective in vitro against *C. albicans* in a biofilm than was amphotericin B or fluconazole (12), which may explain why caspofungin eradicated *C. albicans* from the CSF of our patient. To our knowledge, this is the first case of successful treatment of candidal meningitis by caspofungin therapy.

In conclusion, to make a diagnosis of candidal meningitis, clinical alertness for immunocompromised individuals is essential, and inoculation of a large volume of CSF into an enriched liquid medium will improve the fungal culture yield. Caspofungin can be one of the therapeutic alternatives for candidal meningitis, especially in patients failing to respond or deteriorating during amphotericin B or fluconazole therapy.

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