Candidal Meningitis in HIV-Infected Patients: Analysis of 14 Cases

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Five cases of candidal meningitis in human immunodeficiency virus (HIV)–infected patients have been diagnosed in our hospital. This article describes these cases and reviews another nine previously reported in the literature. Most patients (71%) had at least one well-known predisposing factor for candidiasis. Median CD4 cell count was 135/mm³. Headache and fever, in the absence of focal neurologic signs, were the predominant clinical features. The CSF analysis revealed mild pleocytosis and hypoglycorrachia, indistinguishable from those seen in tuberculous or cryptococcal meningitis. Twelve patients (92%) received amphotericin B for a median of 51 days, in combination with fluconazole. Candida species must be kept in mind as a cause of chronic meningitis in HIV-infected patients who have a known predisposing factor.

Candidal infection of the CNS is an uncommon manifestation of disseminated infection due to Candida species. It usually occurs in immunosuppressed patients [1], in patients treated with broad-spectrum antibiotics, in association with intravenous hyperalimentation, following surgical manipulation of a mucosal site colonized with Candida species, or following a neurosurgical procedure [2, 3]. It has also been described as a complication of intravenous drug abuse [4]. Clinicopathologic forms of candidal CNS infection include diffuse cerebritis with microabscesses, parenchymal abscesses, vasculitis, and meningitis [5].

Although candidiasis is the most frequent fungal infection in patients with HIV infection or AIDS [6], in most cases it involves only the foregut (mouth, pharynx, and esophagus). CNS candidiasis seems to be an exceptional complication of HIV infection: Levy et al. [7] reported 5 cases among 366 neurologically symptomatic HIV-infected patients, including 4 with brain abscesses and 1 child with AIDS and probable candidal meningoencephalitis. Furthermore, in an autopsy series of 121 HIV-infected patients with CNS involvement, Koppel et al. [8] reported only one case of multiple candidal brain abscesses.

This study presents five cases of candidal meningitis in HIV-infected adults and reviews those previously reported in the literature, in order to characterize the clinical features and outcome of candidal meningitis in this population.

Patients and Methods

We reviewed retrospectively the medical records of all HIV-infected patients with candidal meningitis at the Ramón y Cajal Hospital diagnosed from January 1990 through April 1996. We noted risk factors for HIV infection, predisposing factors for invasive candidiasis, clinical course, laboratory findings, treatment, and outcome.

Criteria for the diagnosis of candidal meningitis were: (1) isolation of Candida species in CSF culture or histopathologic evidence of candidiasis in meningeal tissue and (2) clinical and CSF findings suggestive of meningitis, in addition to the presence of systemic candidiasis, diagnosed by isolation of the yeast from an extracranial site; clinical and CSF improvement due to antifungal therapy; and exclusion of other pathogens. We defined as chronic meningitis the presence of symptoms suggestive of meningitis for at least 1 month before diagnosis [9].

A review of the published reports of candidal meningitis in HIV-infected adults was performed. MEDLINE was searched for the years 1983–1996 and included articles in all languages. This review was supplemented by examination of major textbooks and follow-up of additional references quoted in the articles located. For the purpose of this review, cases with evidence of parenchymal abscesses were excluded.

Results

Patients. From January 1990 to October 1996, five cases of candidal meningitis among HIV-infected patients were identified at our institution, which represented 0.11% of all HIV-infected individuals seen during that period. Table 1 summarizes their clinical and laboratory features. No brain abscesses due to Candida species were identified in our population. Data from these five patients plus the nine patients [10–18] identified by literature search form the basis for this review.

Twelve patients were males, and the mean age was 30 years (range, 25–50 years). Risk factors for HIV infection were intravenous drug abuse in 11 cases (79%), heterosexual intercourse in 14 cases (93%), and 1 child with AIDS and probable candidal meningoencephalitis. The mean CD4 cell count was 135/mm³. Headache and fever, in the absence of focal neurologic signs, were the predominant clinical features. The CSF analysis revealed mild pleocytosis and hypoglycorrachia, indistinguishable from those seen in tuberculous or cryptococcal meningitis. Twelve patients (92%) received amphotericin B for a median of 51 days, in combination with fluconazole. Candida species must be kept in mind as a cause of chronic meningitis in HIV-infected patients who have a known predisposing factor.
The median CD4 cell count, among the eight patients for whom this determination was available at the time of admission, was 135/mm$^3$ (range, 25–312/mm$^3$).

Only five patients (36%) had had a prior AIDS-related opportunistic disease at the time of diagnosis. Eight patients had previous episodes of mucosal candidiasis. A history of at least one predisposing factor for systemic or CNS candidiasis was noted in 10 of the cases (71%): active intravenous drug addiction in 9 (64%) and a ventriculoperitoneal shunt (in place at the onset of meningitis) in 1. The most frequent Candida species involved was Candida albicans (13 cases, including our 5 patients), while Candida tropicalis was isolated in only 1 case.

**Clinical presentation.** Headache (13 cases; 93%) and fever (12 cases; 86%) were the most frequent symptoms, with a mean duration of 58 days before admission (range, 12–365 days). Nuchal rigidity was observed in seven patients (50%). Four patients had altered mental status, usually disorientation or confusion, but focal neurological signs were rare: two patients each presented with a third-nerve palsy and diplopia, because of poor response, whereas the other refused amphotericin therapy.

**Microbiological studies.** Blood cultures were negative for 1. During follow-up, one patient had a relapse of candidal meningitis 150 days after therapy had a relapse of candidal meningitis 150 days after the first episode.

<table>
<thead>
<tr>
<th>Patient's age (y)</th>
<th>Risk factor</th>
<th>Duration (d)</th>
<th>Clinical feature(s)</th>
<th>CSF findings</th>
<th>Therapy (total dose, mg)</th>
<th>Follow-up (mo)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>39/M VP shunt</td>
<td>52</td>
<td>30</td>
<td>Headache</td>
<td></td>
<td>AmB (786)</td>
<td>17/S</td>
<td></td>
</tr>
<tr>
<td>27/M IVDU</td>
<td>25</td>
<td>30</td>
<td>Fever</td>
<td></td>
<td>AmB + 5FC (1,250)</td>
<td>4/D</td>
<td></td>
</tr>
<tr>
<td>29/M IVDU</td>
<td>40</td>
<td>12</td>
<td>Fever, headache</td>
<td></td>
<td>AmB (2,000)</td>
<td>48/S</td>
<td></td>
</tr>
<tr>
<td>29/M IVDU</td>
<td>312</td>
<td>30</td>
<td>Fever, headache</td>
<td></td>
<td>AmB + 5FC (2,500)</td>
<td>12/S</td>
<td></td>
</tr>
<tr>
<td>28/M IVDU</td>
<td>224</td>
<td>30</td>
<td>Fever, headache</td>
<td></td>
<td>AmB + 5FC (1,000)</td>
<td>24/S</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** AmB = amphotericin B; D = died; SFC = 5-fluorocytosine; IVDU = intravenous drug use; S = survived; VP = ventriculoperitoneal.
Discussion

In contrast with other immunocompromised individuals, candidal meningitis is a rare event in patients with AIDS. Despite decreased candidicidal activity [19], AIDS itself is not considered a full risk factor for disseminated candidiasis, because the cellular defect is related to T lymphocytes more than to neutrophils and macrophage function. Not surprisingly, 71% of patients in this review had a known predisposing factor for candidal meningitis, which might have contributed to the acquisition of CNS candidal infection. All but two cases have been reported from Spain, suggesting a higher incidence of this complication in a determined geographic area.

However, the predominant risk factor for HIV infection in Spain is intravenous drug abuse, and systemic candidiasis in addicts who use brown heroin in fresh lemon juice has been described [20]. This fact, along with the relatively low incidence of candidal meningitis in our HIV-infected patients with variable levels of immunodepression, suggests that the association of spontaneous candidal meningitis and HIV infection, in the absence of predisposing factors to candidiasis, is possible but uncommon.

Although direct inoculation following lumbar puncture or after ventriculoperitoneal shunt placement has been described [21], the exact pathogenesis of candidal meningitis remains unknown. The likely route of infection in cases of disseminated candidiasis is hematogenous spread from a variety of peripheral sites of active candidal infection, as it has been described in previous studies in non-HIV-infected patients, who present with CNS involvement in 48%–71% of cases [22, 23].

Although blood cultures were negative, we believe that this was the cause of meningeal involvement in most of our patients and that it was related to the high frequency of intravenous drug addiction. Accidental inoculation of Candida species from the skin during the diagnostic lumbar punctures is not likely because (1) the patients’ CSF findings were compatible with meningitis from the time of the first lumbar puncture, (2) other pathogens were excluded, and (3) they responded to antifungal treatment.

Most patients in this study had symptoms for >4 weeks before admission, suggesting that a subacute or chronic course is also the usual form of presentation of candidal meningitis in HIV-infected patients. Mild lymphocytic or polymorphonuclear pleocytosis, a raised protein level, and hypoglycorrachia were the predominant CSF findings, abnormalities indistinguishable from those noted with tuberculous, cryptococcal, and even bacterial meningitis, which occur more frequently in HIV-infected patients [7, 8].

Empirical tuberculous treatment was started for 50% of patients before a definitive diagnosis, and even in three patients the adenosine deaminase activity value was >10 IU/L, a cutoff with high specificity for the diagnosis of tuberculous meningitis [24]. Therefore, definitive diagnosis of candidal meningitis needs to be documented by culture; culture of a large volume of CSF [25], CSF filtration and subsequent culture of the sediment, or direct inoculation in hypertonic media may be necessary [26].

In our series there were two patients with systemic candidiasis and chronic meningitis whose CSF cultures did not yield a Candida species. Despite the frequency of coinfection in AIDS patients, the lack of another diagnosis and the response to antifungal treatment suggested the diagnosis of candidal meningitis. Cryptococcal meningitis was unlikely in these patients because both had a high CD4 cell count, a situation in which cryptococcosis is very uncommon [27]. These two cases show that deep-tissue candidiasis may be associated with CNS infection and that therefore the isolation of Candida species organisms from any site in the body bespeaks potential CNS involvement.

The most appropriate treatment for candidal meningitis has not been established. Smego et al. [28] recommended combined therapy with amphotericin B and flucytosine, because this combination is associated with rates of survival of 88%. However, the optimal cumulative dose of amphotericin B is unknown, and several cases were managed before flucytosazole was available. In spite of its high activity against most strains of Candida and its excellent CSF penetration, the role of flucytosazole has not been subjected to controlled evaluation in humans.

In our series, one patient was cured with flucytosazole therapy, while another had to be switched to treatment with intravenous amphotericin B. In animal studies, higher efficacy in terms of meningeal sterilization was found with use of amphotericin B than with flucytosazole [29]. The failure of flucytosazole treatment in a child with candidal meningitis, attributed to the high MIC, has also been reported, although he had a ventriculoperitoneal shunt that was not removed [30].

Intrinsic resistance of C. albicans to flucytosazole in vivo is unusual, unless the isolate is derived from a patient receiving long-term suppressive therapy with this agent [31]. We suggest that while results of further studies are pending, amphotericin B plus flucytosine remains the initial treatment of choice for candidal meningitis. In our experience, the rate of survival found with this regimen was 70%, a figure very similar to that noted in recent series in which amphotericin B and flucytosazole were available [25, 28].

One study reported that a prolonged course before diagnosis; hypoglycorrachia; and the presence of intracranial hypertension or focal neurological deficits were risk factors for increased mortality in cases of candidal meningitis [22]. Because of the low number of cases reported and the variability in CD4 cell counts, we could not assess any prognostic factor among HIV-infected patients with candidal meningitis.

Characteristically, maintenance antifungal treatment was given to 63% of the patients. Although the rate of relapse in this population is unknown, suppressive treatment with flucytosazole was used in our five cases, despite clinical and mycologic response, because of the persistence of CSF abnormalities and subjacent immunodepression. The patient who stopped taking
maintenance therapy relapsed in a few days. It seems reasonable to continue treatment for an extended period beyond the point of clinical improvement.

References