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

Jose L. Casado, Carmen Quereda, Jesús Oliva, Enrique Navas, Ana Moreno, Vicente Pintado, Javier Cobo, and Iñigo Corral

From the Departments of Infectious Diseases and Neurology, Hospital Ramón y Cajal, Madrid, Spain

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 hypoglycorrhachia, indistinguishable from those seen in tuberculous or cryptococcal meningitis. Twelve patients (92%) received amphotericin B for a median of 51 days, in combination with flucytosine in five cases. The overall mortality among treated patients was 31%. Although the risk of relapse of candidal meningitis is unknown, maintenance antifungal therapy was given to seven patients (63%), usually 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.

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 with an HIV-infected patient in 1 (7%); and unknown in 2.
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, respectively. Cerebral CT scanning showed meningeal enhancement in 1 patient and hydrocephalus in 3 (21%); 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.

CSF findings. CSF pleocytosis (<500 cells/mm$^3$) was noted in all cases. The CSF WBC counts ranged from 7 to 346/mm$^3$, with a median of 78/mm$^3$ before treatment, and with a polymorphonuclear cell predominance in eight patients (57%). The CSF glucose level was <40 mg/dL in 11 patients (78%), and the median CSF protein level was 83 mg/dL (range, 23–580 mg/dL). Of the eight patients for whom adenosine deaminase activity was determined, two (25%) presented with a value of >10 IU/L.

Microbiological studies. Blood cultures were negative for all patients. The diagnosis was initially made by gram staining of CSF for 28.5% of patients (four cases). A Candida species was recovered from the CSF of 11 patients (79%) after a median time of 6 days (range, 1–40 days) and usually after repeated spinal taps. Two patients had candidal meningitis diagnosed—despite the fact that CSF cultures were negative—because extracranial candidiasis was proved by isolation of C. albicans from a costochondral node, by response to antifungal therapy, and by exclusion of other pathogens.

One patient’s candidal meningitis was diagnosed at autopsy. CSF cultures for bacteria, mycobacteria and other fungi, and latex agglutination cryptococcal antigen were negative. In the five cases diagnosed at our institution, CSF abnormalities persisted despite clinical improvement. Three patients’ CSF parameters completely normalized after a median of 6 months.

Therapy and outcome. One patient died before diagnosis and specific antifungal treatment (diagnosis was made at autopsy). Of the 13 patients treated, 12 (92%) received amphotericin B, and 6 received it in combination with oral fluconazole. One patient received both intrathecal and intravenous amphotericin B. The total dose of amphotericin B ranged from 786 to 2,500 mg. Two patients received treatment with fluconazole: one was switched to treatment with intravenous amphotericin B because of poor response, whereas the other refused amphotericin B therapy and then received oral fluconazole (resulting in adequate evolution).

Seven patients (50%) were initially thought to have tuberculous meningitis and received specific therapy for a mean of 22 days (range, 7–40 days). There were four deaths among treated patients; the overall mortality due to candidal meningitis was 31%. Of these four patients who died despite treatment, only two lived long enough to receive a course of antifungal therapy similar in length to that of the survivors. One patient’s death, 4 months after diagnosis, was due to cerebral infarction attributed to candidal meningitis.

Median duration of follow-up was 395 days (range, 15–1,395 days). Maintenance therapy, given to 7 patients for a median of 110 days (range, 30–1,325 days), was with fluconazole in 5 cases, ketoconazole in 2, and weekly amphotericin B in 1. During follow-up, one patient had a relapse of candidal meningitis 55 days after the interruption of maintenance therapy with fluconazole, but it abated with a new course of combined treatment. Another patient not receiving secondary prophylaxis had a relapse of candidal meningitis 150 days after the first episode.

Table 1. Clinical and CSF characteristics of five HIV-infected patients with candidal meningitis at the authors’ facility.

<table>
<thead>
<tr>
<th>Patient’s age (y)</th>
<th>Sex</th>
<th>Risk factor</th>
<th>CD4 cells (no/mm$^3$)</th>
<th>Duration (d)</th>
<th>CSF findings</th>
<th>Follow-up (mo)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>39/M</td>
<td>29/M</td>
<td>VP shunt</td>
<td>52</td>
<td>30</td>
<td>Headache</td>
<td>160</td>
<td>17</td>
</tr>
<tr>
<td>27/M</td>
<td>29/M</td>
<td>IVDU</td>
<td>25</td>
<td>30</td>
<td>Fever</td>
<td>83</td>
<td>4</td>
</tr>
<tr>
<td>29/M</td>
<td>29/M</td>
<td>IVDU</td>
<td>40</td>
<td>12</td>
<td>Fever, headache</td>
<td>182</td>
<td>48</td>
</tr>
<tr>
<td>28/M</td>
<td>29/M</td>
<td>IVDU</td>
<td>321</td>
<td>30</td>
<td>Fever, headache</td>
<td>84</td>
<td>12</td>
</tr>
<tr>
<td>27/M</td>
<td>29/M</td>
<td>IVDU</td>
<td>224</td>
<td>30</td>
<td>Fever, headache</td>
<td>580</td>
<td>24</td>
</tr>
</tbody>
</table>

NOTE: AmB = amphotericin B; D = died; 5FC = 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 fluconazole was available. In spite of its high activity against most strains of Candida and its excellent CSF penetration, the role of fluconazole has not been subjected to controlled evaluation in humans.

In our series, one patient was cured with fluconazole 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 fluconazole [29]. The failure of fluconazole 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 fluconazole 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 fluconazole 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 fluconazole 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