Treatment of meningeal coccidiomycosis with liposomal amphotericin: case report

Manuel Alberto Cano Rangel, Norberto Gómez Rivera, Roberto Dorame Castillo, Jesús Contreras Soto and Sandra Talamante

Abstract

Background. Coccidioidomycosis was first described in the late 18th century by Alejandro Posadas. The first case in Sonora was reported in 1948 by Madrid. Coccidioidomycosis is caused by both species of a dimorphic fungus, one limited to the California area (C. immitis) and the other a non-California strain (C. posadasii).

Clinical case. A 6-year-old male patient from Caborca, Sonora, presented headache and projectile vomiting. At 2½ years of age he was treated at a hospital with the diagnosis of undetermined hydrocephalus. At 3½ years of age, a diagnosis of coccidioidal meningitis was made without knowing the serum antibody and cerebrospinal fluid (CSF) titers. He received treatment with fluconazole for 3 years with 1 month of amphotericin B deoxycholate. Upon admission to our hospital, elevated antibody CSF titers were present.

Conclusion. After being treated with liposomal amphotericin (2 mg/kg) for 9 months, he reached a total dose of 5 475 mg, presenting good clinical outcome with decreased serum antibodies and CSF titers. During his treatment no clinical or laboratory data suggested toxicity due to liposomal amphotericin administration.

Key words: coccidioidomycosis, cerebrospinal fluid, fluconazole, liposomal amphotericin.

Introduction

Coccidioidomycosis was first described in 1892 in an Argentine soldier by Alejandro Posadas; later Rixford and Gilchrist described in 1896 the organism in California. In Sonora, the first case that occurred was published in 1948 by Gaston Madrid.

Coccidioidomycosis is a deep mycosis caused by a dimorphic fungus of the genus Coccidioides spp. of which two species are known: one restricted to the area of California called C. immitis and the other non-California species known as C. posadasii. This pathology is restricted to the Western hemisphere.

In the early 20th century, Ophulos first described clinical coccidioidal meningitis, and Ryfkogel subsequently associated it with hydrocephalus.

Coccidioides spp. meningitis is the most feared clinical presentation, occurring months or years after primary infection occurs. It is spread from a primary focus, which is commonly the lung, through lymphatic or lymphohematogenous route. Before the existence of antifungal therapy, death occurred in a few months, although some patients were known to survive for >2 years.
Without doubt, treatment of coccidioidal meningitis is the most important factor for positive prognosis. Fifty years ago, Williams administered intrathecal amphotericin B deoxycholate, which was the gold standard for many years. Subsequently, treatments were proposed with azoles such as miconazole and intrathecal regimens with high-dose ketoconazole. In 1988, fluconazole was initially used with historic results that exceeded those of intrathecal amphotericin. However, this therapy is not considered curative and requires lifelong treatment.

Recently published studies have demonstrated the potential usefulness in the treatment of meningeal infections by Coccidioides spp. with liposomal amphotericin. This report describes a patient with meningeal coccidioidomycosis who was successfully treated with liposomal amphotericin.

Clinical case
We present the case of a 6-year-old male patient who was a native and resident of Caborca, Sonora, an area located in the north of the state. He began with headaches accompanied by projectile vomiting at 2½ years of age and was taken to the local hospital.

He was diagnosed with hydrocephalus of undetermined origin and a ventriculoperitoneal shunt valve was placed. Two months later he continued with symptoms characterized by headache and projectile vomiting and was diagnosed with frontal subdural hematoma requiring surgical treatment. The valve was replaced due to dysfunction on eight occasions.

Diagnosis of coccidioidomycosis was established at 3½ years of age without knowing the serum antibody titers and cerebrospinal fluid (CSF) and intradermal reaction to coccidioidin. He was managed with fluconazole for 3 years at 6 mg/kg/day. He received, in association with fluconazole, a scheme of amphotericin B deoxycholate for a month but relapsed again with the same clinical data.

He was brought to our institution for a second opinion with the following clinical data upon admission. On physical examination he was conscious, irritable, with headache, eyes deviated to the right outwards and downwards, decrease in right arm strength and ataxic gait.

Laboratory tests were positive for antibodies on admission in CSF (lumbar) and serum, negative CSF (ventricular). Table 1 summarizes the evolution of serum and CSF antibodies during treatment.

Regarding cytochemical analysis, it was only able to be obtained in the last sample, showing xanthochromic aspect, elevated protein and cellularity 2/mm³. Once positivity was demonstrated for infectious activity in the CSF, treatment was started with liposomal amphotericin (AmBisome, Astellas Pharma US, Deerfield, IL) at 2 mg/kg with an administration time of 9 months, reaching a total cumulative dose of 5 475 mg at a dose of 182 mg/kg. No significant renal toxicity data were observed. Table 2 shows the evolution of the markers of renal toxicity.

Table 1. Evolution of serum antibody titers and CSF at initiation, during, and at the end of treatment with liposomal amphotericin

<table>
<thead>
<tr>
<th>Date</th>
<th>Sample type</th>
<th>Precipitin</th>
<th>Complement fixation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/7/2007</td>
<td>Serum</td>
<td>+</td>
<td>1:16</td>
</tr>
<tr>
<td>5/7/2007</td>
<td>CSF (lumbar)</td>
<td>ND</td>
<td>1:16</td>
</tr>
<tr>
<td>1/24/2008</td>
<td>CSF (ventricular)</td>
<td>ND</td>
<td>&lt;1:1</td>
</tr>
<tr>
<td>2/27/2008</td>
<td>Serum</td>
<td>+</td>
<td>1:4</td>
</tr>
<tr>
<td>2/27/2008</td>
<td>CSF (valvular)</td>
<td>ND</td>
<td>1:1</td>
</tr>
<tr>
<td>6/19/2008</td>
<td>Serum</td>
<td>-</td>
<td>1:2</td>
</tr>
<tr>
<td>6/19/2008</td>
<td>CSF (valvular)</td>
<td>ND</td>
<td>&lt;1:2</td>
</tr>
<tr>
<td>6/19/2008</td>
<td>CSF (lumbar)</td>
<td>ND</td>
<td>1:2</td>
</tr>
</tbody>
</table>

ND, no data; CSF, cerebrospinal fluid.
Clinical outcome was towards improvement, decreasing neurological symptoms, headache disappearing, and serum titer and lumbar CSF antibodies being negative.

Discussion
Coccidioidomycosis is a fungal infection found endemically in parts of Mexico. Gonzalez-Ochoa has identified three main regions: the northern region that includes northern Baja California, Sonora, Chihuahua, Nuevo Leon and Tamaulipas, the Pacific coastal area that extends to include parts of Sonora, Guerrero, Sinaloa, Nayarit and Jalisco and, finally, the central zone stretching from Coahuila, Nuevo Leon, Durango and San Luis Potosi.3 Caborca, Sonora, the residence of our patient, is located in the north and is also consistent with that described by Saubolle, as this area is located at the bottom of the so-called “Sonoran Desert Life.”1,2

In 2002 it was reported that there were two closely related fungal species referred to as Californian strains (C. immitis) and non-Californian (C. posadasii); however, previous studies by Burt and Koufopanou already established differences.5,6 We infer that the species infecting our patient was C. posadasii.

It is rare to find clinical descriptions of coccidiodal meningitis in children. Catanzaro, in a series of cases of disseminated disease in children, showed that the trend is of a subacute nature, evolving over weeks.8 Symptoms include headache, vomiting, convulsions and stiff neck. There was a significant delay in establishing the diagnosis in our patient because it was made nearly a year after presenting a blockage in the CSF circulation. Royce considers hydrocephalus to be a late clinical manifestation of the disease.7 On the other hand, we do not really know the characteristics of the patient’s meningeal inflammation before admission to our hospital, no doubt an important issue to discuss as a suspected diagnosis. At the time of admission to our institution, the patient presented after 3 years of therapy with irritability, headache, and the third cranial nerve injury, accompanied by ataxic gait, as described by some authors.7

Diagnosis of meningitis is established by demonstrating the presence of the fungus in CSF by direct observation or in culture media. Given the difficulty of establishing the diagnosis by these methods, it is virtually established by the identification of complement-fixing antibodies.7,10 In our patient, after 3 years of treatment with fluconazole and a course of amphotericin B deoxycholate (IV) for 1 month, evidence of complement-fixing antibodies frankly elevated in serum and lumbar CSF were found, but not in the ventricular CSF. This is particularly true for azole therapy, as it is considered not curative and should be administered for life.9

Amphotericin B is a polyene antibiotic synthesized by Streptomyces nodosus. It acts by binding to ergosterol in the fungal cytoplasmic membrane creating pores in the cell membrane, with loss of cellular organelles and finally cellular lysis.11 However, limiting its use is liver and kidney toxicity. In an effort to maintain its pharmacological spectrum, lipid-
Based formulations have been developed that share the same spectrum but with less drug toxicity. Having overcome the most important obstacles of liver and kidney toxicity of amphotericin B deoxycholate, administration of liposomal formulation of amphotericin (AmBisome) demonstrates potential utility in the treatment of meningeal infections by Cryptococcus neoformans, Candida albicans and in experimental rabbit studies, to lessen the burden of colony-forming units of the fungus in CSF.

In our patient, AmBisome was administered over a period of 9 months. There was significant clinical improvement, disappearance of irritability and headache, and adequate ambulation, which is associated with decreased serum antibody titers and also in the CSF (Table 1).

During treatment there were no data of liver or kidney toxicity. The patient showed a decrease in the levels of SGOT, SGPT (liver enzymes) and serum creatinine, maintaining stable potassium levels.

Toxicity data from a clinical standpoint are decrease in levels of potassium and doubling of baseline creatinine because the known mechanisms of nephrotoxicity due to amphotericin B are involvement of smooth muscle cells of tubules and arterioles, causing vasoconstriction and, consequently, defects in tubular transport and duplication of basal creatinine. None of these data were present in our patient.

In Sonora, coccidioidomycosis is not a disease of mandatory reporting, so lack of knowledge about it causes delay in diagnosis and treatment. For this reason, establishment of continuing medical education strategies and establishment of a program aimed at primary care units will allow us to achieve better results.

Correspondence to: Dr. Manuel Alberto Cano Rangel
Servicio de Infectología
Hospital Infantil del Estado de Sonora
Hermosillo, Sonora, México
E-mail: drcano61@hotmail.com

References