



Case Report

Trending serial CSF samples to guide treatment of refractory coccidioidal meningitis with intrathecal liposomal amphotericin

Brian Fiani^{a,*}, Alvin Nguyen^b, Syed A. Quadri^c, Mudassir Farooqui^d, Atif Zafar^d, Ajeet Sodhi^a, Shubha Kerkar^e, David Nacionales^a, Glenn M. Fischberg^a

^a Department of Neurosurgery, Desert Regional Medical Center, Palm Springs, CA, USA

^b Department of Neurology, Desert Regional Medical Center, Palm Springs, CA, USA

^c Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

^d Department of Neurology, University of New Mexico, Albuquerque, NM, USA

^e Infectious Disease, Desert Regional Medical Center, Palm Springs, CA, USA



ARTICLE INFO

Keywords:

Coccidioidal meningitis
Amphotericin B
Liposoma amphotericin B
Azoles
Intrathecal
Refractory meningitis

ABSTRACT

Intrathecal amphotericin B deoxycholate (AmB-d) can be prescribed as an adjunct to systemic therapy for severe or recalcitrant cases coccidioidal meningitis. Recently intravenous (IV) Liposomal amphotericin B (L-AmB) has been recommended as monotherapy therapy for refractory coccidioidal meningitis based on its advantages over (AmB-d), however, its intrathecal use has not been reported. Moreover, there is nothing in the literature quantifying clinical improvement with objective laboratory data in human patients. Consequently, there are no guidelines on how to monitor regularly for improvement of coccidioidal meningitis with treatment of intrathecal L-AmB. The present case addresses both of these. We report intrathecal use of L-AmB for refractory coccidioidal meningitis. Our data demonstrate that there is a correlation between clinical improvement and a decrease in cerebrospinal fluid (CSF) white blood cells (WBC's), protein, and coccidioidal titers with treatment of intrathecal L-AmB with serial collection of CSF studies at the same site, in our case via collection through an external ventricular drain (EVD). As a result, one may postulate that serial CSF collection can be used to monitor the treatment of coccidioidal meningitis; however this case also addresses the risk of developing ventriculitis with sustained EVD placement.

1. Introduction

Coccidioidal meningitis is a rare and lethal complication of coccidioidal infection resulting in death in 95% of patients within two years if left untreated. This is further complicated by not only delayed treatment as diagnosis is not often straight forward, but also by patients who are refractory to standard therapy.

Treatment guidelines for coccidioidomycosis recommends fluconazole 400 mg PO daily for patients not severely ill but can go up to 800 mg or 1000 mg daily [1]. Patients on long-term triazole therapy may experience refractory or relapsing disease even with documented compliance. These cases can become challenging to manage due to disease severity and lack of substitute treatment options. Therefore, for such cases guidelines suggest that intrathecal amphotericin B deoxycholate (AmB-d) can be used in addition to fluconazole with dosing ranging between 0.01 mg and 1.5 mg per dose daily to weekly, starting at a low dose increasing until intolerance appears, and it can be given

either through the cistern or ventricles. However, there are no specific guidelines suggesting an end goal to therapy including recommendations on what to look for diagnostically to evaluate for improvement with treatment [1].

Previously amphotericin B treatment in rabbit models has shown benefits of both IV liposomal amphotericin B (L-AmB) and amphotericin B lipid complex as options to treat coccidioidal meningitis with clinical improvement along with a decrease in coccidioidal colonies seen in treatment groups versus control groups [2]. Recently IV L-AmB monotherapy therapy has been reported for refractory coccidioidal meningitis, offering a potential additional treatment option for relapsed or disease not responding to chronic triazole therapy [3]. However, the intrathecal use of L-AmB for severe or recalcitrant coccidioidal meningitis cases has not been established. Here the authors share their experience of successfully treating a case of coccidioidal meningitis refractory to oral fluconazole therapy with intrathecal L-AmB as well as trending serial cerebrospinal fluid (CSF) samples at the same site, via

* Corresponding author at: Desert Regional Medical Center, 1180 N. Indian Canyon Dr. Ste. 214 W, Palm Springs, CA, 92262, United States.
E-mail address: bfiani@outlook.com (B. Fiani).

<https://doi.org/10.1016/j.clineuro.2019.03.019>

Received 10 May 2018; Received in revised form 3 January 2019; Accepted 27 March 2019

Available online 05 April 2019

0303-8467/ © 2019 Elsevier B.V. All rights reserved.



Fig. 1. CT head performed after EVD placement for hydrocephalus which was on hospitalization day two. Catheter placement and ventriculomegaly are seen.

collection through an external ventricular drain (EVD) to evaluate and guide with the treatment.

2. Case report

A 44 year old man with past medical history of coccidioidal meningitis diagnosed almost two years earlier, compliantly taking fluconazole 400 mg daily presented to us with persisting headache, worsening mental status, and seizures; symptoms suggesting persisting coccidioidal meningitis refractory to scheduled 400 mg fluconazole. The patient was found to have hydrocephalus on a brain CT so an EVD was placed (Fig. 1).

Infectious Disease was subsequently consulted and the patient's fluconazole was increased to 800 mg daily. Despite improvement in hydrocephalus and a higher dose of fluconazole, symptoms were not significantly improved. Hence, it was decided that patient would subsequently receive 1.5 mg amphotericin injections through his EVD with serial CSF analysis prior to each injection in hopes of improving his symptoms as well as his CSF profile (Table 1). Fluconazole 800 mg was used daily ever since admission until discharge in addition to

Table 1

The data reflects the CSF content, showing no significant downtrend in any parameters except for percentage in lymphocytes after increasing oral fluconazole from 400 mg daily to 800 mg daily for two weeks. However, there was a significant downtrend in WBC, RBC and protein levels after intrathecal amphotericin was administered for approximately 6 weeks. Immediate uptrend in WBC and protein after onset of ventriculitis was observed. Notice the lumbar puncture sample after removal of EVD and treatment of ventriculitis reflects a distribution much different than that collected from the EVD.

Timeframe of CSF	Week 1	Week 3 (Increase Flucanazole)	Week 9 (Intrathecal Amphotericin)	Week 9 (After Ventriculitis)	Week 10 (LP Sample)
WBC	186	301	0	90	97
RBC	1122	3914	10	1	170
Lymphs (%)	76	19	0	5	41
Glucose	45	37	48	< 20	91
Protein	2152	1967	146	439	> 3000
IgG	9.7	NC	0.2	0.4	2.6
IgM	NC	NC	0.2	0.4	2.6
Coccidioides Ab Quant	1:32	NC	1:32	1:16	1:8
CSF Culture	Negative	Negative	^a Light <i>Corynebacterium striatum</i>	^b Rare <i>Corynebacterium striatum</i>	Negative

NC = not collected.

LP = lumbar puncture.

IgG/IgM = total IgG/IgM not EIA anti-coccidioidal IgG/IgM.

^a Light *Corynebacterium striatum* = light growth of *Corynebacterium striatum*.

^b Rare *Corynebacterium striatum* = rare growth of *Corynebacterium striatum*.

intrathecal L-amb that was given every 2–3 days. L-AmB was preferred over deoxycholate amphotericin B because of its less nephrotoxicity and multiple advantages over AmB-d.

Patient became more stable with significant improvement in mental status while receiving amphotericin B injections over the course of 6 weeks and our plan at the time was to have an Ommaya reservoir placed for continued regularly-scheduled L-AmB injections with close follow up of neurological status and CSF studies as an outpatient via serial lumbar punctures. Unfortunately, the patient developed ventriculitis after prolonged EVD placement for almost two months and as a result, the EVD was promptly removed and the patient was no longer a candidate for Ommaya reservoir placement. A CSF sample was thereafter collected from a lumbar puncture with the content of the study being noticeably vastly different from that of CSF previously collected from the ventricles. The patient was subsequently discharged after the ventriculitis was treated on fluconazole 800 mg orally daily and has remained free of relapse since 2 years. The lumbar CSF was not retested because he was lost to follow up for 2 years and was recently seen in the clinic with no history of relapse during this period.

3. Discussion

Although IV AmB-d is effective in many CNS fungal infections it has not shown to be as efficient in the treatment of CNS coccidioidal infections [1]. However, it can be prescribed intrathecally as an adjunct to systemic therapy for the treatment of severe or refractory CNS coccidioidal cases. The intrathecal administration of AmB-d requires considerable expertise and the patient tolerance also varies. On the other hand L-AmB offers numerous advantages over AmB-d in the treatment of aggressive CNS mycoses. Compared to AmB-d, the L-AmB formulation has been found to achieve high concentrations in the reticuloendothelial system, attain higher blood concentrations and a higher mean area under the curve [2,3]. It exhibits better pharmacokinetics and decreased clearance compared with other lipid preparations and has been found to be less nephrotoxic than AmB-d [4]. Moreover, L-AmB formulations are cost-effective, have fewer infusion-related reactions, better CNS penetration and have demonstrated to be more effective for treatment of various fungal infections than AmB-d [4]. However there is not much literature available on the safety, efficacy, or tolerability of L-AmB in the treatment of coccidioidal meningitis.

The treatment of coccidioidal meningitis with L-AmB was shown to improve morbidity and mortality significantly in rabbits [2]. This can be attributed to the fact that lipid formulations have the capability to easily infiltrate monocytes and be carried to the infection site thus raising the local concentration of amphotericin B [2]. Stewart et al.

successfully treated two patients with drug refractory coccidioidal meningitis using IV L-AmB monotherapy, demonstrating an additional option for salvage of recalcitrant coccidioidal meningitis cases [3]. Before our case intrathecal use of L-AmB as a treatment option for coccidioidal meningitis has not been examined. Our decision was based on the non-improving condition of our patient along with less toxicity and advantages of L-AmB over AmB-d.

Serial CSF studies, from when amphotericin injections were first initiated until right before the patient developed a complication from ventriculitis, reflected an overall downtrend in WBC's, RBC's and protein level, which are suggested to be the most important CSF parameters, especially WBC. The patient was correspondingly observed to have an overall improvement in neurological status along with improvement of hydrocephalus. In the literature regarding treatment of coccidioidal meningitis in rabbit models, it was similarly demonstrated that treatment with amphotericin B resulted in decrease in WBC's as well as clinical improvement [2]. As decreasing WBC's correlated with decreasing fungal colonies in animal models, one may infer that there was also a reduction in fungal colonies in our patient when his WBC's decreased. In accordance, our patient's coccidioidal titers, which have previously been reported to be a good diagnostic tool for coccidioidal meningitis [5], were also observed to downtrend from 1:32 to 1:8 throughout his hospital stay. In review of the data (Table 1), one could also infer that the trend in RBC's and protein could be indirect markers that may reflect the clinical status of someone with coccidioidal meningitis, noting that the trending of RBC's have not been reported in previous case reports or guidelines as a tool for clinical correlation.

Although our case showed that having an EVD in place makes it much easier to draw CSF as well as inject amphotericin B, it nevertheless serves as an entry point for infection and unfortunately, after being in place for almost two months, our patient did indeed develop ventriculitis. One way to combat this is to consider placing an Ommaya reservoir and remove the EVD as soon as possible, which was considered in our case, but was unfortunately planned for the day following onset of ventriculitis. A downside to this would be that it would make it more difficult to trend CSF labs regularly. One could make an effort to draw CSF regularly through repeated lumbar punctures although the content of the samples will likely be very different from that obtained from the ventricles, as reflected in the rabbit studies [2]. Toward the end of this admission, we collected a sample from a lumbar puncture after the EVD was removed due to ventriculitis and the content was very different from that seen in our serial CSF studies from the

ventricles. This could be explained by the ventriculitis altering the CSF content but could be attributed to the different distribution of CSF content in the lumbar region versus the ventricles, a phenomenon that was also seen in the rabbit studies. Hence, it is important that when trending serial CSF studies that the content be collected from the same region, whether it be from the ventricles or the lumbar spine.

4. Conclusion

Our case demonstrates intrathecal L-AmB as a valid treatment of choice for coccidioidal meningitis refractory to oral fluconazole. This case very closely reflects the results seen in rabbit models in terms of both CSF analysis as well as clinical improvement, suggesting that serial CSF content specifically WBC and coccidioidal titers can be used as a tool to monitor for clinical improvement.

Conflict of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Funding source/disclosure

The authors have not received any funding for this work from any organization.

References

- [1] J.N. Galgiani, N.M. Ampel, J.E. Blair, A. Catanzaro, F. Geertsma, S.E. Hoover, R.H. Johnson, S. Kusne, J. Lisse, J.D. MacDonald, S.L. Meyerson, P.B. Raksin, J. Siever, D.A. Stevens, R. Sunenshine, N. Theodore, 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis, *Clin. Infect. Dis.* 63 (6) (2016) 112–146.
- [2] K.V. Clemons, J. Capilla, R.A. Sobel, M. Martinez, A.J. Tong, D.A. Stevens, Comparative efficacies of lipid-complexed amphotericin B and liposomal amphotericin B against coccidioidal meningitis in rabbits, *Antimicrob. Agents Chemother.* 53 (5) (2009) 1858–1862.
- [3] E.R. Stewart, M.L. Eldridge, I. McHardy, S.H. Cohen, G.R. Thompson, Liposomal amphotericin B as monotherapy in relapsed coccidioidal meningitis, *Mycopathologia* (2018) 1–4.
- [4] J.W. Hiemenz, T.J. Walsh, Lipid formulations of amphotericin B: recent progress and future directions, *Clin. Infect. Dis.* 22 (Suppl. 2) (1996) S133–S144.
- [5] C. Kassis, S. Zaidi, T. Kuberski, A. Moran, O. Gonzalez, S. Hussain, C. Hartmann-Manrique, L. Al-Jashaami, A. Chebbo, R.A. Myers, L.J. Wheat, Role of coccidioides antigen testing in the cerebrospinal fluid for the diagnosis of coccidioidal meningitis, *Clin. Infect. Dis.* 61 (10) (2015) 1521–1526.