CLINICAL VIGNETTE

Use of Retromastoid Cisternal Ommaya Reservoir for Intrathecal Administration of Amphotericin in Treating Severe Refractory Coccidioides Meningitis

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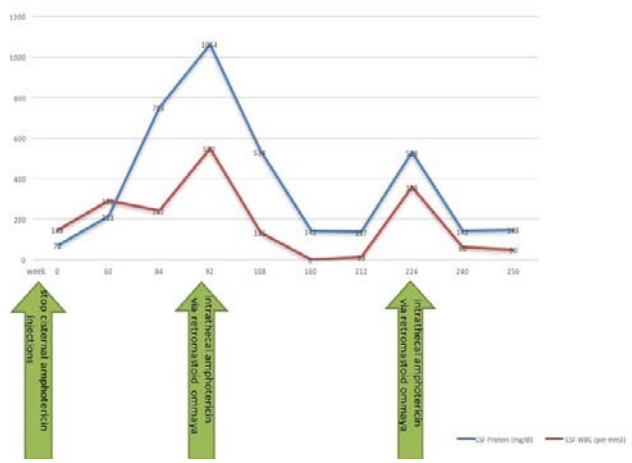
Introduction

Refractory Coccidioides meningitis remains a clinical dilemma with limited treatment options. Fluconazole is effective in controlling disease in most patients; however, there are patients who progress despite appropriate anti-fungal treatment. This can result in severe neurologic morbidity or even death.[1,2] Current expert recommendations include fluconazole initially then, if needed, employing advanced azoles such as voriconazole or posaconazole for refractory disease.[3-5] Despite the efficacy of these medications in controlling disease in most patients, there are still patients who have progressive basilar disease with severe racemose cisternal involvement. Amphotericin and liposomal amphotericin intravenously has been used for refractory cases of meningitis with overall poor response to IV amphotericin administration. Intrathecal amphotericin has been utilized with improved efficacy in severe refractory cases, however, administration of intrathecal amphotericin can be problematic. It is an invasive procedure usually done by cisternal injection, carrying the risk of possible injury to the vertebral arteries, essentially limiting the procedure to tertiary centers with neurosurgical back-up. Also, arachnoiditis is a common side effect. Lumbar injections via lumbar reservoirs are more practical but also are complicated by arachnoiditis and have unreliable penetration of amphotericin superiorly to the basal cisterns where infection lies.[6,7] Intraventricular ommaya reservoirs also have the problem of delivery of amphotericin to the basal cisterns and are not useful when a VP shunt is present.[8] Here is a case of severe refractory coccidioides meningitis in which multiple complications occurred with standard azole treatment, necessitating intrathecal amphotericin. Intrathecal amphotericin administered via direct cisternal injections resulted in improvement of CSF parameters but was complicated by severe arachnoiditis requiring cessation of treatment with subsequent disease progression. Use of a retromastoid cisternal ommaya reservoir for amphotericin delivery resulted in improvement in clinical and CSF parameters, minimal side effects, much improved comfort for the patient, with long lasting control of infection. This case demonstrates that with severe refractory coccidioides meningitis where intrathecal amphotericin is necessary, delivery by a retromastoid ommaya reservoir may be the procedural method of choice. It appears safe and comfortable relative to other means of intrathecal amphoteric administration and appears to control meningitis at least as well as cisternal injections.

Case Report

A 25-year-old female had been suffering with severe refractory coccidioides meningitis for about 3 years. She had numerous hospitalizations due to progression of symptoms despite standard fluconazole dosing. She was then switched to a combination of voriconazole with intravenous liposomal amphotericin. Despite this treatment, her clinical signs worsened with the progression of chronic nausea, headache and diplopia. She had continued elevation of CSF protein and pleocytosis with no improvement. She began to show signs of increasing hydrocephalus on imaging and she was referred for Ventriculo-Peritoneal shunting and cisternal injection of intrathecal amphotericin. Patient had some initial discomfort with the procedure but did have significant clinical improvement with CSF showing decreased protein and white blood cells. Unfortunately, gradually, neurologic signs consistent with arachnoiditis developed and increased despite administration of glucocorticoids. Eventually with each injection, the patient would develop lower extremity paralysis lasting for 1-2 weeks. Because of this she decided to stop all cisternal injections and continued on oral posaconazole only. Soon after, she again had clinical deterioration with renewed headache, nausea and diplopia. Protein and white blood cells again began to elevate in the CSF. At this point the only treatment option appeared to be reinstitution of intrathecal amphotericin. It was recommended she have placement of a retromastoid ommaya reservoir as described by Wrobel and Alksne.[8] Administration of intrathecal amphotericin was started, initially daily for the first week increasing the dose .2 mg daily until 1 mg was tolerated, then continued 3 times a week for 30 days then weekly for 30 days. The patient had rapid improvement in clinical symptoms with only minimal side effects of flushing but no other observable neurologic effects or arachnoiditis. Her CSF parameters improved dramatically (**Figure 1**) and she remained clinically stable for 1 year. At about 1 year post-treatment, the patient again began to develop increasing headache and nausea. Repeat CSF showed increased protein and pleocytosis and it was felt to be due to progression of the coccidioides meningitis. Administration of intrathecal amphotericin via her retromastoid ommaya reservoir was reinstituted. The patient again responded well with relatively no side effects and she has now remained symptom free with stable CSF protein and CSF white blood cells.

Fig. 1. Response of CSF parameters to administration of intrathecal amphotericin via retromastoid ommaya reservoir



Discussion

Coccidioides meningitis is a severe chronic fungal infection that can produce dense cisternal exudate potentially leading to CSF obstruction, hydrocephalus, arachnoiditis, vasculitis and cranial neuropathies. Often there is severe morbidity and even death in uncontrollable cases. Fluconazol is currently recommended based on expert opinion and limited clinical trials. Unfortunately, there are some patients whose infection progresses despite adequate therapy.[1,2] There are a few case studies demonstrating successful treatment with advanced azoles after fluconazole failure. Other antifungals such as intravenous amphotericin show poor efficacy and a high rate of adverse events. The echinocandin class of antifungals may show some efficacy in limited coccidioides case studies but they do not seem effective in meningitis likely due to poor CSF penetration and variability of coccidioides sensitivity.[3-5] With these severe refractory cases, intrathecal delivery of amphotericin appears necessary. For over 40 years, clinicians have had experience with intrathecal amphotericin for the treatment of coccidiodes meningitis with a few limited trials showing survival benefit. A number of techniques have been developed to deliver intrathecal amphotericin. Intraventricular ommaya reservoirs, direct cisternal injection via cervical puncture, direct lumbar injection via lumbar reservoirs have all been used.[6,7] The technique of retromastoid ommaya reservoir placement described by Wrobel and Alksne is much easier than prior midline suboccipital ommaya reservoirs which were difficult to insert surgically and much more difficult to palpate and administer drug.[8] This method has now been used in a number of cases by Moran and Smith with practically no side effects or complications.[9,10] Intrathecal therapy will likely continue to be necessary for refractory coccidioides meningitis. This case study and the work by Moran and Smith suggest that retromastoid ommaya placement may be the procedure of choice to administer intrathecal amphotericin with more comfort for the patient, less risk of complications and similar efficacy.

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