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Case Report: Central Nervous System Toxicity Associated with Liposomal Amphotericin B Therapy for Cutaneous Leishmaniasis

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Abstract. AmBisome (liposomal amphotericin B) is used for prophylaxis and treatment of fungal infections, treatment of visceral leishmaniasis, and more recently, treatment of cutaneous leishmaniasis. Although the package insert cites neurologic toxicities in up to 20% of cases, review of the literature did not reveal any specific cases describing this side effect, particularly in a patient without comorbidities. We describe a healthy 38-year-old male treated with liposomal amphotericin B for cutaneous leishmaniasis acquired during military duties in Iraq. Shortly after completion of his treatment course, he reported memory difficulties and confusion. Further evaluation revealed no other source, and his cognitive issues were attributed to liposomal amphotericin B toxicity. These issues resolved over a few weeks, which is consistent with data about the drug's tissue penetration and metabolism available in the literature. This is a potential side effect of liposomal amphotericin B that can be observed in otherwise healthy patients.

INTRODUCTION

Cutaneous leishmaniasis, which is caused by several *Leishmania* species and transmitted by the bite of the sandfly, is endemic in the tropics and subtropics, including areas in Iraq and Afghanistan where US military troops are deployed. The clinical spectrum of disease can vary, with most infections remaining asymptomatic, but it can include cutaneous disease, which initially appears as erythema that can develop into a papule and progressively ulcerate over weeks to months.[1] Although lesions can self-cure, many are treated to accelerate healing, improve cosmetic outcome, and prevent parasitic spread or relapse. The World Health Organization recommends treating with pentavalent antimonial drugs, such as sodium stibogluconate, which carry several significant toxicities including pancreatitis, transaminitis, and significant myalgias and arthralgias. Given these toxicities as well as other issues with its administration, such as need for prolonged intravenous therapy, alternative therapies for cutaneous leishmaniasis are being sought. Other treatments used worldwide include miltefosine, fluconazole, cryotherapy, thermotherapy, and more recently, liposomal amphotericin B, which is already approved by the US Food and Drug Administration for treatment of visceral leishmaniasis. Although there are no randomized, controlled trials using liposomal amphotericin B (AmBisome; Astellas Pharm US Inc., Deerfield, IL) for this indication, there are several case series in the literature detailing its efficacy, with toxicities described including, most commonly, infusion reactions, renal dysfunction, cytopenias, and gastrointestinal upset.[2–6] In a recent study, 84% of 19 patients with cutaneous leishmaniasis treated with liposomal amphotericin B (3 mg/kg per day) for a median of seven doses experienced cure with their initial treatment course.[7]

Amphotericin B deoxycholate, a polyene antimicrobial agent, has been in use since the 1950s, mainly to treat fungal infections. Its common toxicities are well-described in the literature and include infusion-related reactions with fevers and chills, renal dysfunction, cytopenias, and nausea/vomiting. Given these toxic side effects, less toxic lipid formulations have been approved and are in widespread use in the United States today. In 1997, the US Food and Drug Administration approved liposomal amphotericin B for the treatment of visceral leishmaniasis, although its use for cutaneous leishmaniasis is still off-label and not currently recommended by the World Health Organization for Old World cutaneous leishmaniasis.[8] After the success that our military colleagues have had using liposomal amphotericin B to treat cutaneous leishmaniasis at their military treatment facility, our patient with cutaneous leishmaniasis was treated with AmBisome but developed confusion and forgetfulness after completion of therapy.[7]

CASE REPORT

This patient was a previously healthy 38-year-old male who was deployed to Iraq for military operations. While in Iraq, he was bitten by insects while on patrol and subsequently, noted onset of papules that enlarged and ulcerated into six discrete lesions located on his wrist, forearm, cheek, flank, and bilateral thighs. After unsuccessful response to two courses of antibiotics, a skin biopsy was performed, with findings consistent with cutaneous leishmaniasis. Given several indications for treatment, including location and number of lesions, the patient was admitted to the hospital and treated with liposomal amphotericin B (3 mg/kg) intravenously (IV) daily with dose-escalating infusion for 7 days.[7] He was hydrated with normal saline before each infusion and pre-medicated with acetaminophen and diphenhydramine. He was on no other medications chronically and took no other medications while hospitalized other than the ones noted above. He tolerated the therapy without difficulty or evidence of toxicity on his daily complete blood count or chemistry during therapy. His lesions began to dry up and appeared to be improving.

However, on follow-up evaluation 1 week after completing the liposomal amphotericin B, the patient reported new difficulty with remembering numbers, including passwords and phone numbers, and was having trouble recognizing ranks on uniforms. He stated that it took him several attempts to correctly dial his wife's phone number. He also stated that he had difficulty recognizing which button to push in the elevator, and consequently, he got off on the wrong floor and wandered around for 10 minutes before remedying this mistake. He denied this ever happening previously and denied prior head

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injury, trauma, or involvement in any blasts while deployed to the war zone. He had no past history of any psychiatric diagnoses, such as depression or anxiety, and had not been diagnosed with post-traumatic stress disorder. He scored 27 of 30 on a mini mental status exam, with points off for being unable to remember two words at 1 minute and for not being able to complete serial sevens. A full neurologic exam was normal to include normal visual acuity. Screening laboratory tests, including thyroid-stimulating hormone, rapid plasma reagin, vitamin B12 level, and human immunodeficiency virus enzyme-linked immunosorbent assay (HIV ELISA), were all within normal limits. These symptoms continued for approximately 2 weeks after completion of the liposomal amphotericin B and then resolved completely over the following week.

DISCUSSION

In this case report, we present a patient with central nervous system (CNS) cognitive effects that may have been caused by liposomal amphotericin B. Liposomal amphotericin B is generally used to treat fungal infections, including infections caused by *Aspergillus* and *Candida* species and Cryptococcal meningitis. It is also used to treat visceral leishmaniasis, and there is a growing body of data showing that it can be used to treat cutaneous leishmaniasis as well. Although the package insert for liposomal amphotericin B does note anxiety, confusion, and thinking abnormalities in up to 20% of drug recipients, these rates are similar to those with conventional amphotericin B and therefore, are difficult to ascribe to AmBisome itself, and we have not seen these neurologic adverse events in otherwise healthy patients.

There are two case reports that describe CNS toxicity associated with conventional amphotericin B deoxycholate. In the first, a patient being treated for pulmonary cryptococcosis (*Torula granulomas*) experienced altered mental status, weakness, and later, flaccid paresis and tremor in association with use of amphotericin B.[9] The amphotericin was discontinued. Cerebrospinal fluid (CSF) studies were within normal limits. The patient continued to decompensate and died 5 days after cessation of the drug. There were no CNS abnormalities found on autopsy, including no evidence of brain or spinal cord torulosis, although special staining of the peripheral nerves showed myelin degeneration that was felt to be consistent with a toxic reaction to amphotericin B. The second case involved a patient that experienced acute dysphoria, agitation, confusion, and suicidal ideation after IV administration of amphotericin B for disseminated histoplasmosis.[10] This patient was not felt to have CNS histoplasmosis and also had a normal CSF evaluation and electroencephalogram. Although this patient remained hospitalized and on amphotericin B for the duration of the treatment course, after completion of therapy, his mental status returned to baseline.

Based on animal studies, we know that liposomal amphotericin B does, in fact, penetrate into the brain, although at much lower tissue levels than into the liver, kidneys, and spleen. It has been shown to accumulate in brain tissue of uninfected rabbits to a greater degree than other lipid formulations of amphotericin B or conventional amphotericin B, and its distribution in the brain is increased by inflammation.[11,12] An autopsy study of seven patients treated with liposomal amphotericin B for suspected or proven invasive fungal infections supports this conclusion, with the highest liposomal amphotericin B levels in the liver and spleen followed by kidney, lung, myocardium, and brain.[13,14] Animal studies have showed that liposomal amphotericin B has sustained tissue levels, with one study showing its retention in the kidney and spleen for up to 2 weeks post-treatment and another noting tissue half-lives of 1–4 weeks.[15,16]

However, despite liposomal amphotericin B being able to distribute in the brain, albeit at low levels, and having a prolonged tissue half-life, cases of neurotoxicity caused by liposomal amphotericin B are not well-described in the literature, despite the package insert for the product noting this potential complication. A randomized trial comparing liposomal amphotericin B to amphotericin B lipid complex for treatment of febrile neutropenia reported confusion in 12.9% of the patients who received liposomal amphotericin B (which was not significantly different from amphotericin B lipid complex). The etiology for the confusion was noted to be unclear; the confusion did not occur with the initial doses, and it was short-lived in all cases, similar to that in our patient.[17] These patients had multiple baseline comorbidities and were on numerous medications, unlike the patient that we describe here. Review of the literature describing use of liposomal amphotericin B for the treatment of visceral or cutaneous leishmaniasis did not reveal any cases of confusion or any neurotoxicity related to treatment.[14,18,19]

Although we cannot definitively prove that our patient's neurologic symptoms were caused by his liposomal amphotericin B treatment, we have no evidence for another more likely etiology by history, exam, and screening laboratories for metabolic causes. The time course over which he experienced this issue is consistent with the description in febrile neutropenic patients above as well as animal data detailing tissue half-lives of the drug. Thus, given this reasonable temporal association and no other explanation based on the patient's clinical state, we believe this is most likely a complication of his use of liposomal amphotericin B. This is a potential side effect for healthy patients receiving liposomal amphotericin B for cutaneous leishmaniasis or other indications.

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REFERENCES

1. Reithinger R, Dujardin J, Louzir H, Pirmez C, Alexander B, Brooker S, 2007. Cutaneous leishmaniasis. *Lancet Infect Dis 7:* 581–596.
2. Paradisi A, Capizzi R, Zampetti A, Proietti I, De Simone C, Feliciani C, Amerio PL, 2005. Atypical multifocal cutaneous leishmaniasis in an immunocompetent patient treated by liposomal amphotericin. *J Infect 51:* e261–e264.
3. Brown M, Noursadeghi M, Boyle J, Davidson RN, 2005. Successful liposomal amphotericin B treatment of *Leishmania braziliensis* cutaneous leishmaniasis. *Br J Dermatol 153:* 203–205.
4. Amato VS, Rabello A, Rotondo-Silva A, Kono A, Maldonado TPH, Alves IC, Floeter-Winter LM, Neto VA, Shikanai-Yasuda MA,

2004. Successful treatment of cutaneous leishmaniasis with lipid formulations of amphotericin B in two immunocompromised patients. *Acta Trop 92:* 127–132.
5. Solomon M, Baum S, Barzilai A, Scope A, Trau H, Schwartz E, 2007. Liposomal amphotericin B in comparison to sodium stibogluconate for cutaneous infection due to *Leishmania braziliensis*. *J Am Acad Dermatol 56:* 612–616.
6. Del Rosal T, Artigao FB, Garcia Miguel MJ, de Lucas R, del Castillo F, 2009. Successful treatment of childhood cutaneous leishmaniasis with liposomal amphotericin B: report of two cases. *J Trop Pediatr 56:* 122–124.
7. Wortmann G, Zapor M, Ressner R, Fraser S, Hartzell J, Pierson J, Weintrob A, Magill A, 2010. Liposomal amphotericin B for treatment of cutaneous leishmaniasis. *Am J Trop Med Hyg 83:* 1028–1033.
8. Meyerhoff A, 1999. U.S. Food and Drug Administration approval of AmBisome (Liposomal Amphotericin B) for treatment of visceral leishmaniasis. *Clin Infect Dis 28:* 42–48.
9. Haber RW, Joseph M, 1962. Neurological manifestations after amphotericin B therapy. *BMJ 1:* 230–231.
10. Weddington WW, 1982. Delirium and depression associated with amphotericin B. *Psychosomatics 23:* 1076–1078.
11. Clemons KV, Sobel RA, Williams PL, Pappagianis D, Stevens DA, 2002. Efficacy of intravenous liposomal amphotericin B (AmBisome) against coccidioidal meningitis in rabbits. *Antimicrob Agents Chemother 46:* 2420–2426.
12. Takemoto K, Yamamoto Y, Ueda Y, 2006. Influence of the progression of cryptococcal meningitis on brain Penetration and efficacy of AmBisome in a murine model. *Chemotherapy 52:* 271–278.
13. Vogelsinger H, Weiler S, Djanani A, Kountchev J, Bellmann-Weiler R, Wiedermann CJ, Bellmann R, 2006. Amphotericin B tissue distribution in autopsy material after treatment with liposomal amphotericin B and amphotericin B colloidal dispersion. *J Antimicrob Chemother 57:* 1153–1160.
14. Coukell AJ, Brogden RN, 1998. Liposomal amphotericin B therapeutic use in the management of fungal infections and visceral leishmaniasis. *Drugs 55:* 585–612.
15. Smith PJ, Olson JA, Constable D, Schwartz J, Proffitt RT, Adler-Moore JP, 2007. Effects of dosing regimen on accumulation, retention and prophylactic efficacy of liposomal amphotericin B. *J Antimicrob Chemother 59:* 941–951.
16. Bekersky I, Boswell GW, Hiles R, Fielding RM, Buell D, Walsh TJ, 2000. Safety, toxicokinetic and tissue distribution of long-term intravenous liposomal amphotericin B (AmBisome): a 91-day study in rats. *Pharm Res 17:* 1494–1502.
17. Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A, L Amph/ABLC Collaborative Study Group, 2000. A randomized, double-blind comparative trial evaluating the safety of the liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. *Clin Infect Dis 31:* 1155–1163.
18. Larabi M, Yardley V, Loiseau PM, Appel M, Legrand P, Gulik A, Bories C, Croft SL, Barratt G, 2003. Toxicity and antileishmanial activity of a new stable lipid suspension of amphotericin B. *Antimicrob Agents Chemother 47:* 3774–3779.
19. Olliaro PL, Guerin PJ, Gerstl S, Haaskjold AA, Rottigen J, Sundar S, 2005. Treatment options for visceral leishmaniasis: a systematic review of clinical studies done in India, 1980–2004. *Lancet Infect Dis 5:* 763–774.