Acute hepatic injury with amphotericin B deoxycholate in an immunocompetent patient

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ABSTRACT

Amphotericin B deoxycholate (AmBd) is rarely used due to its adverse effect profile, which includes nephrotoxicity, infusion-related reactions, and hepatotoxicity. The incidence of hepatotoxicity related to AmBd is 18–23%, but the reports of this adverse effect are mainly in immunocompromised patients receiving chemotherapy. We report a case of AmBd-related acute hepatic injury in an immunocompetent male with multiple medical problems. The patient initially had acute hepatic injury likely caused by poor nutritional status and a diagnosis of failure to thrive, but was recovering. He was also diagnosed with bilateral renal fungal mycetomas and received systemic treatment initially with micafungin and then fluconazole after urine cultures returned with the growth of Candida glabrata. Therapy was expanded to systemic AmBd when the fungal balls persisted. The patient subsequently developed hepatic re-injury with 1 dose of AmBd, and the therapy was discontinued. Caution should be exerted when utilizing AmBd in treating patients with previous hepatic injury.

Key words: Antifungal, Candida glabrata, fungemia, liver dysfunction

INTRODUCTION

The clinical use of amphotericin B deoxycholate (AmBd) is primarily limited due to its adverse effect profile, which includes nephrotoxicity, infusion-related reactions, and hepatotoxicity.[1] Around 18–23% of the patients who receive any formulation of amphotericin B will experience an increase in liver function tests (LFTs), but <1% will actually discontinue therapy due to this elevation.[3] However, most evidence of hepatotoxicity due to amphotericin B is described mainly in oncology patients,[2,3] with few case reports in immunocompetent patients.[4] We present a case of probable AmBd-induced acute hepatic injury in an immunocompetent patient resulting in drug discontinuation.

CASE REPORT

A 39-year-old African-American male was admitted (day 1) from a nursing home for a chief complaint of weakness and decreased appetite for several days. He was initially admitted to the medical Intensive Care Unit for suspected sepsis of unknown origin and was started empirically on vancomycin and meropenem. At
that time, his urine cultures grew >100,000 colony-forming units (CFU)/mL of *Candida glabrata* (sensitivities not performed); however, no antifungal therapy was added to his antimicrobial regimen as this was thought to be colonization secondary to his chronic indwelling Foley catheter for urinary retention. He was stabilized and transferred to the general medical floor on day 6 for further management of his sepsis. Subsequent workup on days 10–13 revealed osteomyelitis due to a Stage IV sacral decubitus ulcer with exposed bone. The patient had negative blood cultures, but urine cultures continued to remain positive now yielding 15,000 CFU/mL of *Candida albicans* (sensitivities not performed) on day 28. This organism was thought to be a colonizer and no treatment was received. The patient was treated for a total of 45 days for his osteomyelitis with a combination of vancomycin and various Gram-negative therapies including meropenem, ertapenem, and ceftazidime.

Concurrently to the patient’s infectious workup, he received a workup for failure to thrive (body mass index 14.7 kg/m²) on day 2 and consequently received a percutaneous endoscopic gastrostomy tube placement on day 12. The patient experienced elevated alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase throughout his hospital course, primarily attributed to failure to thrive and poor nutritional status. The patient was also found to have extremely brittle diabetes with occurrences of multiple hypoglycemic episodes correctable with 50% dextrose boluses. The patient was started on insulin glargine 2 units every evening, but this produced large fluctuations in blood sugars ranging from 18 to 460 mg/dL, with an average of 233 mg/dL. The patient was switched to neutral protamine Hagedorn (NPH) insulin on day 51 at 2 units twice daily in an attempt to avoid hypoglycemia. It was also found that when the patient was not allowed to eat or drink, his blood sugars would drop to <50 mg/dL unless a 5% dextrose infusion was administered. Glycemic goals for this patient were to avoid hypoglycemia and diabetic ketoacidosis, which was extremely difficult despite switching from insulin glargine to NPH insulin.

Despite broad-spectrum antimicrobial treatment for osteomyelitis, the patient continued to have leukocytosis. Subsequent blood and urine cultures were drawn on day 34. On day 36, an abdominal computed tomography (CT) scan was ordered to identify other potential sources of infection. The scan demonstrated right-sided pyelonephritis and left-sided hydronephrosis and hydroureter. The patient’s antimicrobial therapy was expanded to include micafungin. Urology was consulted on day 37 for further management. A repeat abdominal CT scan on day 38 demonstrated pyelonephritis in both kidneys, as well as filling defects (left > right) and mild debris along the bladder base, indicative of fungus balls/mycetomas. On day 40, urine cultures returned growing 35,000 CFU/mL of *C. glabrata* (fluconazole with minimum inhibitory concentration [MIC] of 8 and caspofungin MIC of 0.5 mg/L) and *C. albicans* (fluconazole MIC of 4 mg/L and caspofungin MIC of ≤0.25 mg/L). Blood cultures also returned on day 40 and revealed *C. glabrata* with a fluconazole MIC of 2 mg/L. The patient was switched from micafungin to high-dose fluconazole based on susceptibilities. In addition, urology recommended drainage of the fungal balls and subsequent irrigation with AmBd via bilateral nephrostomy tubes. A nephrostomy tube was placed in his left kidney on day 45 in an attempt to drain the fungal ball and in preparation for AmBd irrigation. After 6 days of systemic antifungal therapy, the blood cultures cleared; however, a renal ultrasound performed on day 54 was still concerning for continued presence of fungal balls. A lack of improvement in renal impairment was observed, indicated by an estimated glomerular filtration rate of 10–30 mL/min/1.73 m², which was comparable to prenephrostomy tube placement. The patient eventually required intermittent hemodialysis on day 56. On day 59, the patient was taken to interventional radiology for possible placement of the right nephrostomy tube; however, this placement failed. The decision was then made to discontinue fluconazole and initiate systemic AmBd at 0.7 mg/kg/day (29.3 mg) to treat the renal fungal balls. On day 61, the patient’s LFTs significantly worsened [Table 1]. This

Table 1: Kidney and liver function test trends leading up to and following amphotericin B deoxycholate administration in a 39-year-old male

| Day of hospitalization | ALP (U/L) | AST (U/L) | ALT (U/L) | Total bilirubin (mg/dL) | Direct bilirubin (mg/dL) | Indirect bilirubin (mg/dL) | Serum creatinine (mg/dL) |
|------------------------|-----------|-----------|-----------|-------------------------|-------------------------|---------------------------|-------------------------|
| Day 51                 | 3982      | 1281      | 910       | 0.35                    | <0.20                   | 0                         | 1.34                    |
| Day 52                 | 3500      | 712       | 715       | 0.41                    | <0.20                   | 0.18                      | 1.37                    |
| Day 53                 | 3042      | 181       | 543       | 0.29                    | 0.23                    | 0                         | 1.32                    |
| Day 54                 | 2819      | 130       | 437       | 0.25                    | <0.20                   | 0                         | 1.25                    |
| Day 55                 | 2284      | 104       | 338       | 0.27                    | <0.20                   | 0                         | 1.08                    |
| Day 56                 | 2221      | 97        | 292       | 0.24                    | <0.20                   | 0                         | 1.14                    |
| Day 57                 | 1993      | 75        | 210       | <0.15                   | <0.20                   | 0                         | 0.85                    |
| Day 59                 | 1943      | 46        | 198       | 0.18                    | <0.20                   | 0                         | 1.14                    |
| Day 61 AmBd initiated  | 1302      | 56        | 92        | 0.34                    | <0.20                   | 0                         | 0.85                    |
| Day 62 AmBd discontinued| 2278      | 838       | 658       | 0.36                    | <0.20                   | 0                         | 1.15                    |
| Day 64                 | 1810      | 81        | 229       | 0.54                    | 0.21                    | 0.33                      | 1.53                    |

ALP=Alkaline phosphatase, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, AmBd=Amphotericin B deoxycholate
was attributed to the AmBd (Naranjo adverse drug reaction probability scale score of 5). The patient’s LFTs returned almost to near baseline, suggesting amphotericin B as the culprit of acute liver injury.

After it was discussed with the patient that all medical treatment options had been thoroughly exhausted, the patient decided to change his code status to do not resuscitate. The patient’s condition continued to decline, and his daughter decided to stop the 5% dextrose infusion that was required to keep his blood glucose normal. The patient expired after 66 days of hospital admission.

**DISCUSSION**

This patient is unique in that he developed renal fungal balls with *C. glabrata*. Development of renal fungal balls in an adult patient is extremely rare; however, risk factors for development include diabetes mellitus, prolonged antibiotic therapy, and malnutrition.[5] Our patient had all the three of these risk factors: Poor glycemic control with extremely brittle diabetes, an extended antibiotic course for osteomyelitis, and significant malnutrition. Primary therapy for fungus balls, especially with *Candida*, includes systemic therapy with amphotericin B +/- flucytosine or fluconazole, but almost always requires an invasive procedure to remove the bulk of the infection.[6] This patient was not stable enough to survive an invasive procedure and had already received 26 days of systemic therapy with micafungin and fluconazole, hence the decision was made to switch to AmBd. AmBd binds to sterols in the cell membranes of fungal and human cells due to its high affinity to biological membranes.[3] It achieves the highest concentrations in the liver, yet actual adverse effects on liver function are rare.[7]

Unfortunately, this patient received one dose of AmBd and developed acute liver injury. While most patients do not require discontinuation of amphotericin due to acute rises in LFTs, caution should be applied to patients with recent liver injury.

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**Conflicts of interest**

There are no conflicts of interest.

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