Reversible cardiomyopathy secondary to Amphotericin-B

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1. Introduction

Amphotericin-B may cause important side effects such as rigors, fever, myalgias, headache, renal dysfunction, and cardiac abnormalities such as bradycardia and other cardiac arrhythmias [1]. There has been a paucity of papers relating Amphotericin-B to cardiomyopathy leading to heart failure. We describe a patient with AIDS with documented congestive heart failure while on Amphotericin-B use with reversion of the cardiac abnormalities after withdrawal of the drug and a switch to fluconazole. This case highlights another important side effect related to Amphotericin-B, a broad antifungal agent.

2. Case

A 32-yr old female patient with AIDS and history of drug abuse was admitted to Hospital Couto Maia, Salvador, Brazil, in December 20th, 2012 (D0) with headache, fever and vomiting. She was diagnosed with cryptococcal meningitis after CSF study showed the following results: 2 cells/mm3, glucose level of 39 mg/dL, protein level of 29 mg/dL, a positive India ink test and a positive CSF cryptococcal antigen detection by the latex agglutination test. She was started on Amphotericin-B deoxycholate (D-Amb) the next day (D+1) at 50 mg per day. Blood samples and CSF were drawn at D0, and they were all positive for yeasts, which were later identified on Sabouraud’s dextrose agar as Cryptococcus neoformans. The patient was not taking antiretroviral drugs, had a CD4+ T cell count of 22 per μL, and a viral load of 163,744 copies per mL (b-DNA) at D+6.

On D+18 the patient presented with dyspnoea, tachypnea, tachycardia (HR=120) and a 3rd heart sound. Chest X-Ray on D+18 showed a diffuse enlargement of the cardiac silhouette (Fig. 1) and a transthoracic echocardiogram (TTE) on D+21 revealed mild enlargement of the left ventricle (LV) and a LV ejection fraction (EF) of 42% alongside a LV fractional shortening of 21%, and a left ventricular end diastolic diameter (LVEDD) of 5.6 cm. Amphotericin-B was discontinued on D+22 and patient was immediately started on Fluconazole therapy at a dose of 1,200 mg per day. After 21 days of Amphotericin-B withdrawal the patient was breathing normally, without dyspnoea, and with normal heart sounds. A new TTE on D+42 revealed a LV EF of 53% and a LVEDD of 5.2 cm. A new X-Ray on D+42 showed a normal cardiac area (Fig. 2). The patient died from neurological complications on D+65...

3. Discussion

Arsura et al. have described a 36-yr old man with dilated cardiomyopathy after 8 months of t-Amb use and a total dose of 2,250 mg that resolved after discontinuation of the drug [2]. Endomyocardial biopsy with electron microscopy showed myocyte hypertrophy with significant loss of myofibrils with no evidence of myocarditis, granulomatous inflammation or other infiltrative process, with findings consistent with toxic cardiomyopathy [2]. Danaher et al. described a 20-yr old man with Coccioides immitis infection treated initially with Fluconazole 900 mg daily with relapse after 6 months [3]. This patient had sternal osteomyelitis and sternal abscess and made use of D-Amb, Amphotericin-B lipid complex, and liposomal Amphotericin-B (LipAmb) and after 55 days of admission he developed cardiac failure that was reversed after withdrawal of the drug and use of cardiac inotropic drugs [3]. Moyssakis et al. described in Greece two patients treated with LipAmb that developed cardiac failure after a few days of use [4]. One patient was a 64-yr old man treated with LipAmb for febrile neutropenia that developed a severe global impairment of the left ventricular function with an ejection fraction (EF) of 13% that returned to 56% after discontinuation of the drug and a second patient was a 23-yr old woman with candiduria that after 8 days of LipAmb use enlargement of the cardiac silhouette (Fig. 1) and a transthoracic echocardiogram (TTE) on D+21 revealed mild enlargement of the left ventricle (LV) and a LV ejection fraction (EF) of 42% alongside a LV fractional shortening of 21%, and a left ventricular end diastolic diameter (LVEDD) of 5.6 cm. Amphotericin-B was discontinued on D+22 and patient was immediately started on Fluconazole therapy at a dose of 1,200 mg per day. After 21 days of Amphotericin-B withdrawal the patient was breathing normally, without dyspnoea, and with normal heart sounds. A new TTE on D+42 revealed a LV EF of 53% and a LVEDD of 5.2 cm. A new X-Ray on D+42 showed a normal cardiac area (Fig. 2). The patient died from neurological complications on D+65...

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developed cardiac failure and an EF of 35% with a return to a near normal function after 1 month of drug withdrawal [4]. More recently, Soares et al. described a 45-yr old man in Brazil that was treated with D-Amb for visceral leishmaniasis for 18 days that presented with cardiac failure after 5 days off the drug with a LVEF of 24% that reversed to normal after 1 month [5]. Table 1 presents these findings for patients with cardiomyopathy related to amphotericin B treatment.

Groot et al. described a 36-yr old man with acute myeloid leukemia and pneumonia due to Absidia corymbifera that on the 24th day of treatment with LipAmb developed ventricular fibrillation just after the infusion [6]. At autopsy no evidence of coronary artery disease or myocarditis was found and the authors discussed that Amphotericin-B may interact with cholesterol-containing human cell membranes, which in turn may result in cellular injury and end-organ dysfunction [6]. That mechanism may in part explain some cases of fatal arrhythmias and, possibly, may be implicated in reversible cardiomyopathy in surviving patients.

Our patient, the 6th documented case in the literature so far, developed signs of cardiac failure after 17 days of D-Amb use that prompted a change in therapy to Fluconazole and a return to normal cardiac function after 21 days of the discontinuation of the drug. An association between Amphotericin-B and hydrocortisone causing reversible cardiac enlargement had been described [7]. However, our patient was not taking corticosteroids at the time of treatment and no cardiac comorbidity was present at admission.

Taking into account the extensive use of amphotericin-B for the treatment of invasive fungal infections in patients with AIDS, infectious diseases clinicians should be aware of the potential for cardiotoxicity when treating patients with this drug.

Conflict of interest

There are none.

### Table 1

Baseline and evolution characteristics reported for patients with cardiomyopathy related to amphotericin B in the literature.

| Patient Age/Gender | Primary diagnosis                  | Indication for AmB use          | Duration of AmB until symptoms onset | Ejection Fraction at cardiac decompensation | Outcome   | Year of publication | Reference cited |
|-------------------|-----------------------------------|---------------------------------|-------------------------------------|--------------------------------------------|-----------|--------------------|----------------|
| 36/Male           | Coccidioidomycosis                | Coccidioidomycosis              | 8 months                            | 32%                                        | Reversible| 1994               | Arsura et al. [2] |
| 20/Male           | Coccidioidomycosis                | Coccidioidomycosis              | 55 days                             | 15–20%                                     | Reversible| 2004               | Danaher et al. [3] |
| 64/Male           | Non-Hodgkins lymphoma             | Febrile neutropenia             | 7 days                              | 13%                                        | Reversible| 2005               | Moysakis et al. [4] |
| 23/Female         | S. pneumoniae empyema             | Candiduria                      | 8 days                              | 35%                                        | Reversible| 2015               | Soares et al. [5] |
| 45/Male           | Visceral leishmaniasis            | Visceral leishmaniasis          | 18 days+5 days (off drug)           | 24%                                        | Reversible|                   |                 |
| 32/Female         | AIDS                              | Cryptococcal meningitis         | 17 days                             | 42%                                        | Reversible| 2016               |                 |

* Amphotericin-B.
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References

[1] P.C. Craven, D.H. Grenillion, Risk factors of ventricular fibrillation during rapid amphotericin B infusion, Antimicrob. Agents Chemother. 27 (1985) 868–871.

[2] E.L. Arsu, Y. Ismail, S. Freedman, et al., Amphotericin B-induced dilated cardiomyopathy, Am. J. Med. 97 (1994) 560–562.

[3] P. Danaher, M. Cao, G. Anstead, M.J. Dolan, et al., Reversible dilated cardiomyopathy related to Amphotericin B, J. Antimicrob. Chemother. 53 (1) (2004) 115–117.

[4] I. Moysakis, T.P. Vassilakopoulos, N.V. Sipsas, et al., Reversible dilated cardiomyopathy associated with amphotericin B treatment, Int. J. Antimicrob. Agents 25 (2005) 444–447.

[5] J.R. Soares, M.C.P. Nunes, A.F. Leite, et al., Reversible dilated cardiomyopathy associated with amphotericin B therapy, J. Clin. Pharm. Ther. 40 (3) (2015) 333–335.

[6] O.A. Groot, R.J. Trof, A.R. Girbes, et al., Acute refractory hyperkalaemia and fatal cardiac arrest related to administration of liposomal amphotericin B, Neth. J. Med. 66 (10) (2008) 433–437.

[7] D.K. Chung, M.G. Koening, Reversible cardiac enlargement during treatment with amphotericin B and hydrocortisone, Am. Rev. Resp. Dis. 103 (1971) 831–841.