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Reversible dilated cardiomyopathy related to amphotericin B therapy

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We describe a patient who developed dilated cardiomyopathy and clinical congestive heart failure after 2 months of therapy with amphotericin B (AmB) for disseminated coccidioidomycosis. His echocardiographic abnormalities and heart failure resolved after posaconazole was substituted for AmB. It is important to recognize the rare and potentially reversible toxicity of AmB.

Keywords: posaconazole, coccidioidomycosis, *Coccidioides immitis*

Introduction

Amphotericin B (AmB) has been associated with a number of adverse cardiac events. Hypertension, hypotension, bradycardia and ventricular arrhythmias have all been reported with its infusion.[1] Although most commonly reported in patients receiving rapid infusions in the setting of renal failure, anuria and hyperkalaemia, arrhythmias have been observed in normokalaemic patients receiving slow infusions. AmB is also known to cause a myopathy mediated by hypokalaemia.[2] Despite these known cardiac toxicities, only a single case of reversible dilated cardiomyopathy secondary to AmB has been reported previously in the literature.[3]

Case report

The voluntary, fully informed consent of the subject described in this research was obtained as required by 32 CFR 219 and AFI 40–402, Protection of Human Subjects in Biomedical and Behavioral Research.

A 20-year-old African–American male presented to an outside facility with fevers, night sweats, cough, myalgias and skin eruptions in the naso-labial fold 10 months after moving to an area endemic for coccidioidomycosis. Culture of, and histopathology from, skin biopsy revealed *Coccidioides immitis*. Serum complement fixation (CF) titre at the time of diagnosis was 1:128 (serological testing was performed by Dr Demosthenes Pappagianis, Coccidioidomycosis Serology Laboratory, University of California-Davis School of Medicine). He was started on fluconazole 800 mg orally once a day.

Six months later, he noted return of fevers, cough and myalgias. He had new complaints of a lump on his sternum and of left knee pain. Physical examination was significant for: a tender, fluctuant sternal mass; a large left knee effusion; and three persistent verrucous lesions in the naso-labial fold. Chest radiography revealed a right upper lobe lung nodule. *C. immitis* was recovered from bronchoalveolar lavage. Fluconazole was stopped and he was started on AmB deoxycholate 0.7 mg/kg (45 mg) per day intravenously, and transferred to Wilford Hall USAF Medical Center.

A staging evaluation revealed an unchanged serum CF titre, the absence of coccidioidal antibodies in the CSF, and lytic lesions in the left distal clavicle and sternum. A CT scan of his chest revealed an 8×4 cm abscess over the sternum (Figure 1). Operative cultures obtained during debridement of these lesions yielded *C. immitis*. Thirty days after admission, it was noted that his creatinine had risen to 1.8 mg/dL and he was switched to AmB lipid complex (Abelcet) at a dose of 5 mg/kg (290 mg) intravenously per day. His creatinine rapidly returned to its baseline of 1.0 mg/dL.

Forty days after admission, magnetic resonance imaging (MRI) of his left knee for recurrent pain and effusion revealed osteomyelitis of the distal femur with a pus collection that had eroded through the lateral condyle via a sinus tract (Figure 2). He underwent radical debridement of his left distal femur 45 days after admission.

The patient developed dyspnoea 55 days after admission. Examination revealed bibasilar crackles and a prominent S3. A transthoracic echocardiogram (TTE) revealed mild enlargement of the left ventricle and an ejection fraction (EF) of 40%–45%. The left ventricular end-

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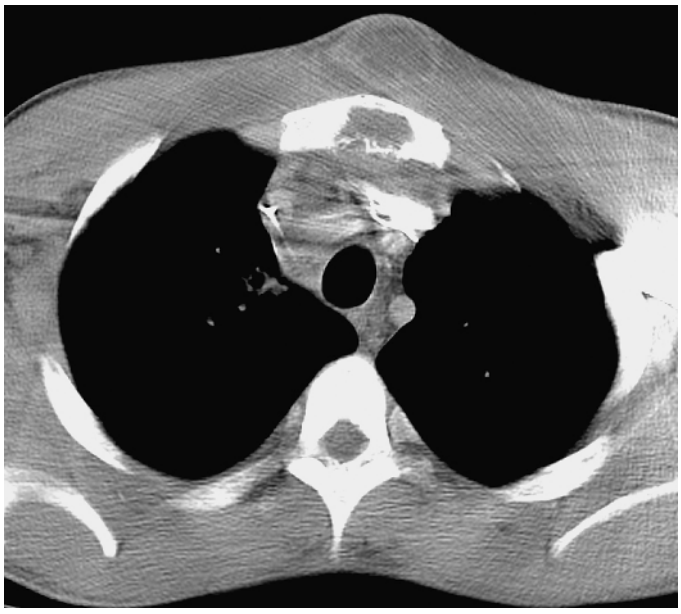

Figure 1. CT scan of the chest showing a lytic lesion in, and an 8 × 4 cm abscess over, the sternum.

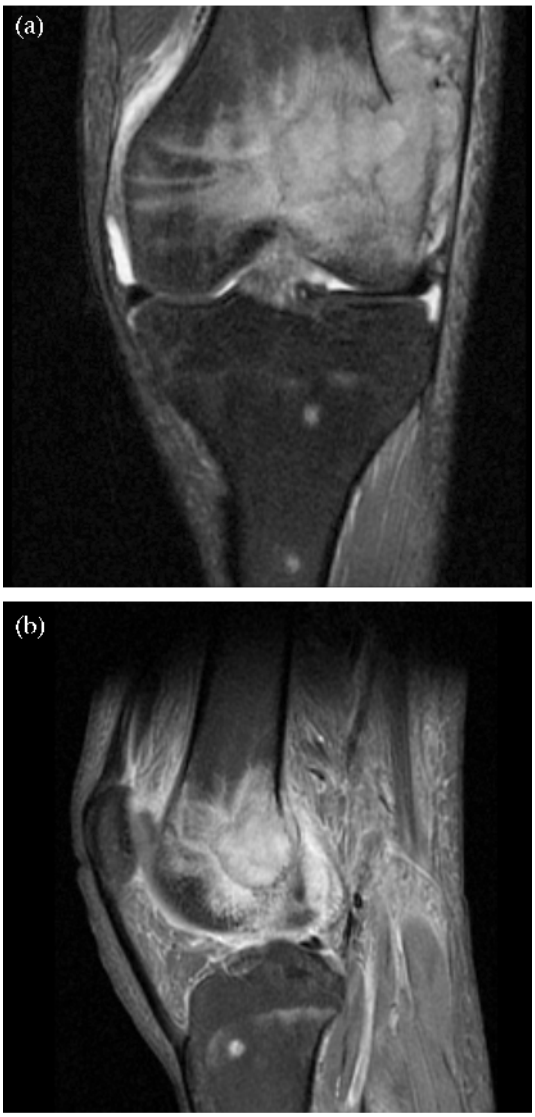

Figure 2. MRI images of the left knee showing osteomyelitis of the distal femur with a pus collection that had eroded through the lateral condyle via a sinus tract: (a) coronal fat-saturated T2-weighted image and (b) sagittal gadolinium-enhanced fat-saturated T1-weighted image.

systolic diameter (LVESD) was 4.1 cm (normal ≤4.0 cm) and the left ventricular end-diastolic diameter (LVEDD) was 5.8 cm (normal ≤5.7 cm). He was treated symptomatically with furosemide.

Overall, persistent fevers, new skin lesions and new foci of bony disease marked his course. TTE was repeated 85 days after admission. This study revealed moderate enlargement of all chambers and an EF of 15%–20%. LVESD was 5.1 cm and LVEDD was 6.3 cm. Lisinopril and digoxin were added. Ninety-one days after admission, AmB liposome (AmBisome) 5 mg/kg (290 mg) intravenously per day was substituted for the AmB lipid complex.

Because of his refractory coccidioidomycosis, and concern that his cardiac dysfunction was due to toxicity of AmB products, treatment with AmB was stopped 99 days after admission, and posaconazole was started on an investigational new drug protocol.[4,5] Within 10 days, his fevers resolved, he gained weight, and the skin and bony disease regressed. Repeat TTE performed 6 weeks later revealed all four cardiac chambers to be of normal size and an EF of 50%–55%. LVESD was 2.1 cm and LVEDD was 4.1 cm.

Discussion

To our knowledge, this is only the second reported case of dilated cardiomyopathy secondary to AmB products.[3] In the first case, endomyocardial biopsy was performed. Light and electron microscopy revealed myocyte hypertrophy with significant loss of myofibrils. In addition, there was significant reduction in the number of mitochondria and significant intramitochondrial cisternal damage. There was no evidence of myocarditis, granulomatous inflammation, haemochromatosis or other infiltrative process. In the light of these pathological findings and because the patient had nearly complete normalization of left ventricular function following discontinuation of AmB, the authors concluded that a toxic cardiomyopathy secondary to AmB was the most likely aetiology.

In 1971, Chung & Koenig[6] reported reversible cardiomegaly and congestive heart failure in three patients receiving AmB and hydrocortisone. They postulated hypokalaemic cardiopathy following salt and water retention secondary to the mineralocorticoid effects of the corticosteroid, coupled with nephrotoxicity from AmB. Cardiac size returned to normal and congestive heart failure resolved within 2 weeks of discontinuing the hydrocortisone; potassium supplements were administered. Subsequent to this case series, synergistic nephrotoxicity during concomitant administration of AmB and corticosteroids was demonstrated in a mouse model.[7] Of note, our patient did not receive hydrocortisone and his potassium was supplemented to maintain normal levels throughout his course.

In addition to the other human case of reversible dilated cardiomyopathy, there are data to suggest that AmB and deoxycholate are directly cardiotoxic. Via its interaction with the cholesterol component of plasma membranes, AmB is known to create pores that are permeable to ions and small molecules. Schanne *et al.*[8] used a frog heart model to show that AmB alters the ionic currents activated

during the cardiac action potential. In an *in vitro* rat heart model, it was shown to induce myocardial toxicity by altering the sarcoplasmic reticular membrane ATPase system.[9] Deoxycholate is an organic detergent known to cause mitochondrial dysfunction and cellular apoptosis.[10] It is unclear whether it is toxic *in vivo* to myocytes.

It is possible that the lipid carriers contained in the AmB preparations received by this patient enhance the cardiotoxicity of the compounds they carry, or are directly cardiotoxic. Whereas peak cardiac tissue concentrations of AmB were similar following equivalent doses of AmB liposome and AmB deoxycholate in a mouse model, prolongation of the interval during which detectable levels of AmB were present in cardiac tissue was seen following administration of AmB liposome (96 h versus 1 h, respectively).[11] This raises the possibility that lipid formulations of AmB may increase the cardiotoxicity of AmB by increasing the duration of exposure. Despite this theoretical concern, existing data regarding two cardiotoxic chemotherapy agents (doxorubicin and daunorubicin) suggest that these carriers actually decrease cardiotoxicity.[12]

Although the lack of endomyocardial biopsy in our case makes it impossible to definitively exclude coccidioidal infection of the heart as the source for the findings in this patient, it seems distinctly unlikely given what is known about such infections. Whereas autopsy studies show that 9%–28% of patients with disseminated coccidioidomycosis have lesions in the myocardium and 5%–14% have lesions in the pericardium, clinical cardiac involvement by this fungus is rare.[13] To date, only 17 cases of pericarditis diagnosed on clinical grounds and/or confirmed antemortem have been described in the literature.[13–16] Three clinical cases of endocarditis have been described in the literature.[17,18] Among these patients, congestive heart failure was the result of constrictive pericarditis or valvular insufficiency. To our knowledge, there are no reported cases of dilated cardiomyopathy secondary to coccidioidomycosis.

Whereas there are a number of hypotheses that potentially explain how AmB might cause this type of cardiotoxicity, it has been in clinical use since 1955 and reports of this phenomenon are rare. Perhaps host factors and duration of therapy play a role. Germane to our case, some studies have shown an excess of idiopathic dilated cardiomyopathy in African–Americans compared with European–Americans.[19] Additionally, given the short duration of therapy for many patients, and the comorbid conditions with which they present (many have underlying heart disease), it seems possible that this phenomenon may simply be under-recognized.

In summary, we describe a case of dilated cardiomyopathy probably secondary to AmB. Because the condition is reversible with cessation of therapy and because a variety of promising new antifungal alternatives are available, it is important to include AmB cardiotoxicity in the differential diagnosis of patients who develop congestive heart failure while receiving it.

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