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Case Report

Drug induced reversible cardiomyopathy reported for liposomal amphotericine B: a rare documented adverse event

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ABSTRACT

Liposomal amphotericin B (LAmB), lipid formulation of amphotericin B (AmB) is used in the treatment of fungal infections, including invasive disease and cryptococcal meningitis and is associated with fewer nephrotoxic and infusion-related adverse effects than conventional amphotericin B. Cardiac toxicity due to LAmB is a rarely reported adverse event in literature. Here we report a case of 53 years female known case of vitiligo, Diabetes mellitus Type 2 diagnosed as case of sinonasal mucormycosis and started on inj LAmB, developed chest pain on day 4 of inj LAmB. ECG and 2D ECHO showed VPBs and ventricular ectopics that were transient and completely recovered on reducing the dose of LAmB. As LV function has recovered on reducing Liposomal AMB, and patient was not on any other cardiotoxic drugs. It was concluded that the patient developed Transient Cardiomyopathy also known as Takotsubo Cardiomyopathy likely due to Liposomal AMB that improved on reducing dose of the drug LAmB. Although very rare but reversible cardiomyopathy also known as Takotsubo Cardiomyopathy due to LAmB is a documented adverse effect. Therefore, ECG monitoring or cardiac monitoring (2D ECHO) should be done when patient is started on LAmB and if at any point cardiotoxicity is suspected then drug should be stopped or reduced in dose immediately. These adverse effects are reversible which recovere on stopping or reducing the dose of LAmB.

Keywords: Hypocalcemia, Parathyroid, Recurrent laryngeal nerve, Thyroidectomy

INTRODUCTION

Amphotericin B, a polyene antifungal agent, is used to treat fungal infections, including invasive disease and cryptococcal meningitis. Liposomal Amphotericin B (LAmB) is a lipid formulation of amphotericin B that alters its pharmacokinetics and thus is associated with fewer nephrotoxic and infusion-related adverse effects than conventional amphotericin B (amphotericin B deoxycholate). The adverse effects that are usually associated with LAmB are Nephrotoxicity, electrolyte abnormalities, infusion-related reactions and sometimes normocytic normochromic anaemia. Cardiac toxicity is a rarely reported adverse event.[1] The cardiac events manifesting with ventricular arrhythmias and bradycardia have been reported in acute overdoses but rarely with conventional dosages and infusion rates.[2]

CASE REPORT

Our patient is a 53-year-old female known case of vitiligo & a newly diagnosed Type 2 DM (uncontrolled) and anaemia was referred to our hospital from a peripheral hospital with a provisional diagnosis of granulomatous disease of the nose.

On Examination of her face, she had collapsed dorsum of the nose (Figure 1). On performing DNE, large septal perforation with crusts was seen with granulations (+) at the edges of perforation. She had a deviation of the angle

of the mouth towards the right with incomplete (L) eye closure and deviation of the tongue towards the right indicating house brackmann recovery grade vi facial nerve palsy (L) and (R) hypoglossal nerve palsy.CECT Nose and PNS revealed heterogeneously enhancing soft tissue seen in the bilateral maxillary sinus with deficiency of the posterolateral wall of the maxillary sinus.

Posteriorly on the right side was peripherally enhancing collection (HU-23) in the retro maxillary space, infratemporal fossa bilaterally (left> right) measuring (182×9×19) mm on the left side and (10×14) mm on right side medially extending into pterygopalatine fossa.

Similar peripherally enhancing small locules in the left medial and lateral pterygoid muscle with associated rarefication of medial and lateral pterygoids.

Thinning and destruction of the nasal septum were noted. CEMRI BRAIN, NOSE, and PNS showed altered signal intensity lesions involving bilateral maxillary sinuses, right frontal sinus anterior and posterior ethmoidal air cells and sphenoid sinus.

Altered signal intensity lesions were noted in the clivus and right paraclival region involving the hypoglossal canal with the encasement of the right hypoglossal canal.

CT-guided Biopsy from B/L ITF for HPE showed features suggestive of Mucormycosis. Her Pre-op 2D-ECHO was normal with an ejection fraction of 60%. The patient was diagnosed as a case of sinonasal mucormycosis extending to the skull base and was started on Inj Amphotericin B Liposomal (LAmB) 300 mg once a day & underwent endoscopic debridement via endonasal transmaxillary trans pterygoid approach (Figure 2 & 3).

She was continued on Inj LAmB 300 mg slow infusion over 4 hours for 3 days. On POD-4, the Patient received her daily dose of LAmb in the evening. She developed chest pain at night. Because of atypical chest pain cardiology referral was done, ECG showed frequent ventricular premature beats (VPBs), and 2D-ECHO showed LV dilated mainly at the apex with an Ejection fraction of 30-35% (Figure 4,5). The patient was diagnosed with dilated cardiomyopathy mild to moderate likely drug-induced.

Electrolytes checked at the time of the cardiac event showed normal serum potassium and sodium levels. She was started on Tab Ecospirin 150 mg OD, Tab Clopid 75 mg OD, Tab Metoprolol 25 mg OD, Tab Ramipril 2.5 mg OD, Tab Lacilactone 40/25mg ½ OD and Inj UFH 5000u sc TDS (for 03 days) and Inj LAmB was reduced to 150 mg daily dose slow infusion. POD-8: She was assessed again by a cardiologist & repeat bedside 2D-ECHO was done. EF was found to improve to 55 %. As LV function has recovered on reducing liposomal AMB, and the patient was not on any other cardiotoxic drugs. It was concluded that the patient developed transient cardiomyopathy also known as takotsubo cardiomyopathy likely due to liposomal AMB that improved on reducing the dose of the drug. In total patient has received a total cumulative dose of 4050 mg of LAmB after which patient was discharged on oral posaconazole after recovery.

During her stay in hospital, there was no fresh episode of any cardiac complaints. The patient has now been on follow-up for 1 year with no residual local or systemic evidence of mucormycosis. Also, there was no change in cardiac function as assessed by the cardiologist.

Figure 1: Collapsed dorsum of nose with HB grade VI facial nerve palsy (Left).

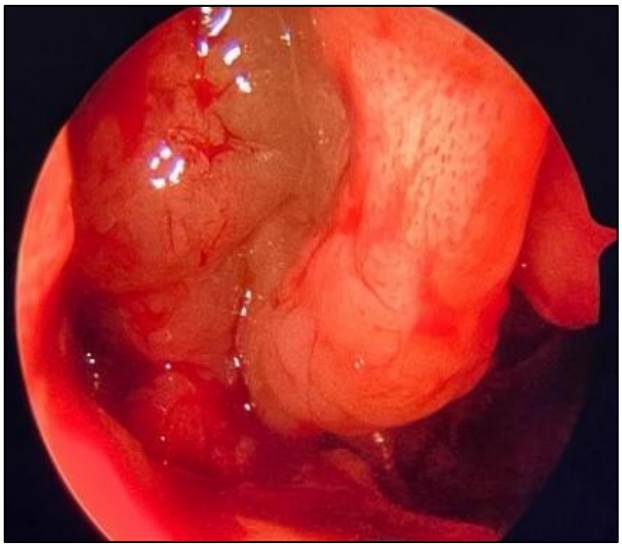

Figure 2: Endoscopic view of polypoidal tissue in right middle meatus.

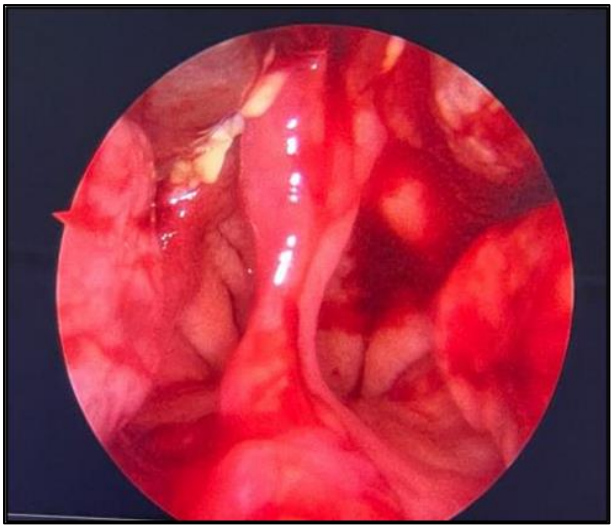

Figure 3: Endoscopic view of fungal debris in right nasal cavity with eroded septum.

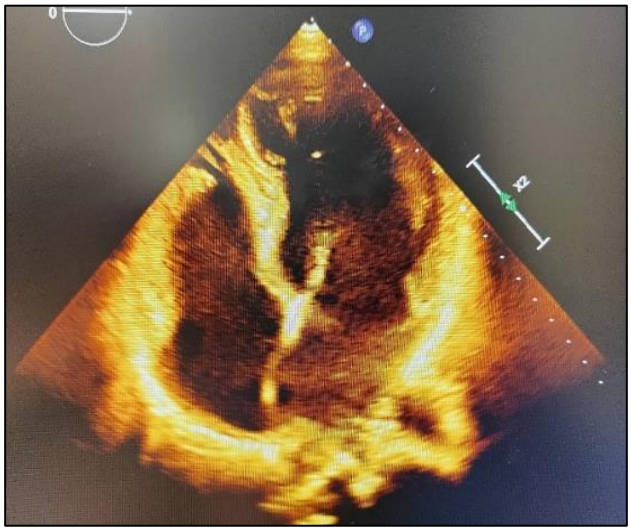

Figure 4: 2D ECHO showing dilated cardiomyopathy and reduced ejection fraction.

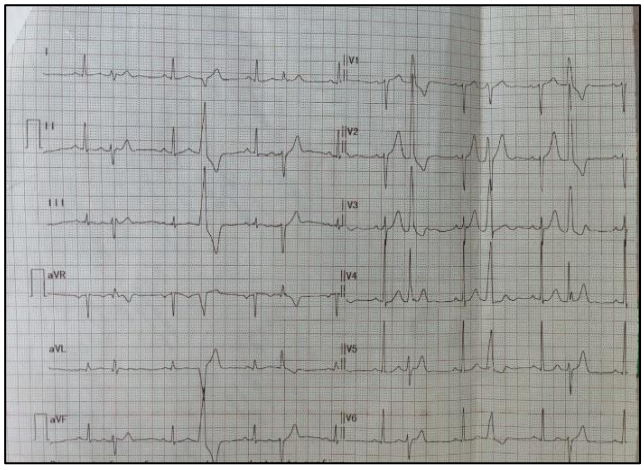

Figure 5: ECG changes with VPBs and ventricular ectopics.

DISCUSSION

Mucormycosis is life-threatening, especially affecting diabetic or immunocompromised patients. The treatment protocols recommend the use of liposomal amphotericin B (≥ 5 mg/kg) combined with surgery whenever possible as first line. Isavuconazole and intravenous or delayed-release tablet forms of posaconazole have remained second-line.[3]

LAmB is a lipid-associated formulation of the broad-spectrum polyene antifungal agent amphotericin B(AmB). It was developed to improve the tolerability profile of amphotericin B deoxycholate, which was considered the gold standard of antifungal treatment for many decades, despite being associated with infusion-related events and nephrotoxicity. The association between AmB and deoxycholate is relatively weak, therefore, dissociation occurs in the blood. AmB acts by binding to the sterol component, ergosterol, of the cell membrane of susceptible fungi.

It forms transmembrane channels leading to alterations in cell permeability through which monovalent ions (NA+, K+, H+, and Cl-) leak out of the cell resulting in cell death. While AmB has a higher affinity for the ergosterol component of the fungal cell membrane, it can also bind to the cholesterol component of the mammalian cell leading to cytotoxicity. The drug itself interacts with both mammalian and fungal cell membranes to damage cells, but the greater susceptibility of fungal cells to its effects forms the basis for its clinical usefulness. The liposome creates a spherical vesicle around the AmB molecules, changing its pharmacokinetics to reduce toxicity by facilitating targeted administration of the AmB by binding to the fungal cell walls, while at the same time protecting human cells from exposure to AmB.

LAmB is rapidly and extensively distributed after single and multiple doses, with steady-state concentrations of AmB attained within 4 days and no clinically relevant accumulation of the drug following multiple doses of 1-7.5 mg/kg/day. No dosage adjustment is required based on age or renal impairment. Typical dosage for LAmB was 3 mg/kg/day. Treatment is generally given for 1-2 weeks. Compared with other AmB formulations, LAmB treatment was associated with a lower incidence of infusion-related adverse events and nephrotoxicity. A higher than recommended dosage of LAmB (10 mg/kg/day) was associated with an increased incidence of nephrotoxicity compared with the standard dosage (3 mg/kg/day), although the incidence of infusion-related reactions did not differ between treatment groups. Severe reactions to LAmB, including anaphylaxis, are uncommon.

Potential cardiac toxicity in the form of transient asystole associated with AmB was first reported in 1983. Since then, a review of the literature has identified nine reports of anaphylaxis or cardiac toxicity attributed to LAmB.[4] It

was noted that all the cases of cardiac toxicity appeared to be dose and time-dependent and were associated with hyperkalaemia.[5] Our patient however did not exhibit hypo or hyperkalemia. In one of the case reports 6 patients in whom AMB or LAmB was given developed reversible cardiomyopathy. In none of these cases, AMB was given for invasive mucormycosis similar to our case.

Electrolyte abnormalities such as hypokalaemia and hypomagnesaemia related to AmB may play a role. However, case reports of arrhythmias in patients with normal concentrations of potassium and magnesium medicated with AmB suggest that it may be directly cardiotoxic. Reversible cardiomyopathy also known as Takosubo Cardiomyopathy is a sudden, transient cardiac syndrome that involves left ventricular apical akinesis and mimics acute coronary syndrome.

CONCLUSION

Although very rare but reversible cardiomyopathy also known as Takosubo Cardiomyopathy due to LAmB is a documented adverse effect. Our Patient presented with chest pain, VPBs and ventricular ectopics that were transient and completely recovered after reducing the dose of LAmB. Therefore, ECG monitoring or cardiac monitoring (2D ECHO) should be done when the patient is started on LAmB and if any point cardiotoxicity is suspected then the drug should be stopped or reduced in dose immediately. These adverse effects are reversible which recovered on stopping or reducing the dose of LAmB.

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