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Liposomal Amphotericin B Induced Pancytopenia- A Rare Case Report

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Abstract

Liposomal amphotericin B (L-AmB) is a lipid-associated formulation of amphotericin B, a broad spectrum anti fungal agent. Even though studies have shown L-AmB to have a much better safety record than the other formulations, several adverse events limits the use of L-AmB to some extent such as hepatotoxicity and also dose dependent anemia and thrombocytopenia. However liposomal amphotericin B induced pancytopenia is rarely seen. Here we report a 58 year old male diagnosed to have hydropneumothorax for which he was treated with IV antibiotics, steroids and oxygen supplementation. Injection Liposomal amphotericin B 5mg/kg was started as prophylaxis for fungal infection. Over a period of 15 days, the blood reports progressively showed abnormal blood counts appearing to be pancytopenia. Hemoglobin levels had dropped to 7.1 g/dl, RBC count decreased to 2.5 M/uL , platelet count to 38,000 cells/mm3, WBC count to 1.53 K/uL and Injection L-AmB was stopped. Management was initiated with several blood transfusions, iron supplementation and a stat dose of s/c erythropoetin injection 4000 IU and Inj Grafeel 300mcg once daily. As the drug was withheld, blood counts gradually improved. Physician should be aware of the risk of hematological toxicities with amphotericin B liposomal and should ensure frequent monitoring of blood counts while administering this drug.

Key Words: Liposomal, amphotericin B, pancytopenia, anemia

INTRODUCTION

Amphotericin B is a amphoteric polyene antibiotic used as a broad-spectrum antifungal agent, with good activity against most fungal species and to treat conditions caused by protozoan Leishmania species.[1,2,3,4,5] It is also used as a prophylactic agent against fungal infections like visceral leishmaniasis in HIV infected patients.[6] Liposomal amphotericin B (L-AmB) is a lipid-associated formulation of this agent.[7,8] The development of this formulation lead to reduced side effects and studies have shown L-AmB to have a much better safety record than both the deoxycholate and lipid complex forms of amphotericin B with fewer infusion-related adverse events and less nephrotoxicity comparatively.[9,10,11] Despite all this, several adverse events limits the use of L-AmB to some extent.[7] The common side effects seen with L AmB are hepatotoxicity, decrease in total protein and serum pottasium and increase in serum creatinine levels and also dose dependent anemia and thrombocytopenia and decrease in WBC count.[9,12] However liposomal amphotericin B induced pancytopenia has not been reported till now.

CASE REPORT

A 58 year old male on anti retroviral therapy and history of recurrent pleural effusion was admitted with complaints of abdominal pain, vomiting and breathing difficulty since 4 days. He was diagnosed to have hydropneumothorax with elevated CRP levels. For this he was treated with IV antibiotics, steroids and oxygen supplementation and started on ATT on suspicion of TB. Injection Liposomal amphotericin B 5mg/kg was started as prophylaxis for fungal infection. As his breathing difficulty did not resolve, pulmonology consultation was sought which advised VATS decortication. Meanwhile his LFTs were progressively increasing over the days in view of which ATT was stopped after 11 days of therapy and the VATS procedure was postponed till the LFTs normalised. Although the LFTs elevations gradually resolved, the blood reports progressively showed abnormal blood counts appearing to be pancytopenia. Over a period of 15 days Hemoglobin levels had dropped to 7.1 g/dl, RBC count decreased to 2.5 M/uL , platelet count to 38,000 cells/mm3, WBC count to 1.53 K/uL. Injection L-AmB was stopped on suspicion of liposomal amphotericin B induced pancytopenia as the reaction was observed during the course of therapy with L-AmB. Management was initiated with several blood transfusions, iron supplementation and a stat dose of s/c erythropoetin injection 4000 IU. Patient was shifted to isolation and Inj Grafeel 300mcg once daily was initiated in view of febrile neutropenia. As the drug was withheld, blood counts gradually improved and patient was discharged with a later date for the procedure as serum bilirubin levels were still elevated.

DISCUSSION

The antifungal activity of Amphotericin B is based on the binding of its hydrophobic moiety to ergosterol moiety of the fungal cell membrane, causing depolarization of the membrane and causes influx of protons and monovalent cations by increasing the membrane permeability, destroying activity and allowing the cytoplasmic contents to leak out, leading to cell death.[13] Studies have observed that the cause for the amphotericin induced anemia appears to be due to reduced production of erythrocytes caused due to either a direct toxic effect on the bone marrow, or secondarily, through amphotericin B induced suppression of erythropoietin production.[14] While others suggest that anaemia caused by L-AmB appears to be haemolytic rather than due to bone marrow depression.[14,15] Shigemi et al suggests that when L-AmB is administered to patients at

doses of >4.0 mg/kg/day and >3.3 mg/kg/day, close attention to a low RBC count and anaemia is needed respectively.[9] Several studies have reported that thrombocytopenia was observed in patients receiving therapy with L-AmB. One study revealed that thrombocytopenia in patients repeatedly receiving L-AmB occurred with high frequency (57.9%). This study also demonstrated that the incidence of thrombocytopenia could be significanly predicted by the dose of L-AmB, and the daily dose of L-AmB inducing thrombocytopenia with 50% probability was 3.0 mg/kg/day. However, the mechanism by which a dose increase can result in thrombocytopenia is not yet understood. Amphotericin B induced leukopenia has been observed with a frequency of 15-17% [16,17,18] Hence it is important to pay attention when patients are receiving L-AmB at doses of greater than 3.0 mg/kg/day for signs of hematological toxicities and even pancytopenia.[19]

CONCLUSION

Here we have observed a rare case of pancytopenia which resolved on witholding the drug given at 5mg/kg once daily for 15 days during the period of which the ADR was observed. Causality assessement using the Naranjo probability Scale yielded a score of 6 indicating a probable case of amphotericin B induced pancytopenia. Physician should be aware of the risk of hematological toxicities with amphotericin B lipsomoal and should ensure frequent monitoring of blood counts while administeirng this drug.

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