Amphotericin B liposome-induced acrocyanosis and elevated serum creatinine

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ABSTRACT

A 77-year-old male patient developed acrocyanosis and pain after treatment with amphotericin B liposome 150 mg daily intravenously for disseminated histoplasmosis, and subsequently developed elevated serum creatinine. Amphotericin B liposome was discontinued, and anisodamine was used intravenously to treat acrocyanosis and pain induced by amphotericin B liposome for 9 days and patient was cured. Naranjo adverse drug reaction probability scale score was 5, the World Health Organization-Uppsala Monitoring Centre criteria: Probable, indicating a probable adverse reaction to amphotericin B liposome.

KEY WORDS: Acrocyanosis, amphotericin B liposome, histoplasmosis, impaired renal function, pain

Introduction

Amphotericin B is a polyene antifungal antibiotic. It has high potent activity against many species of fungi. It is primarily used for the treatment of patients with progressive and potentially life-threatening fungal infections. Its clinical use is often limited by adverse effects, especially dose-dependent nephrotoxicity, and infusion-related reactions. Amphotericin B liposome is developed to reduce nephrotoxicity and infusion-related reactions.[1,2] Other adverse reactions include pulmonary reaction, nausea and vomiting, electrolyte imbalance, and allergic reactions. Here, we report a case of a male patient who developed acrocyanosis and elevated serum creatinine after treatment with amphotericin B liposome. Amphotericin B-related acrocyanosis and pain are rare complications. Potential risk factors in this patient are explored.

Case Report

A 77-year-old, 50 kg male was hospitalized with disseminated histoplasmosis. His medical history included senile degenerative valvular heart disease, premature ventricular contractions, heart function class II (New York Heart Association, NYHA), and anemia. He did not have past history of acrocyanosis, pain, or allergies to other drugs, foods, and pollens. He consumed alcohol and smoking for about fifty years but had given up since 2 years. The patient was treated successfully for disseminated histoplasmosis 1 year ago with intravenous voriconazole, caspofungin acetate, itraconazole, and was prescribed oral itraconazole solution for 10 months on discharge.

The patient presented with persistent pain in the right side of chest and back for 7 days to respiratory outpatient department. He had stopped taking oral itraconazole solution for 2 months. On admission, his vital signs were blood pressure 136/92 mmHg, heart rate 78 beats per min, respiratory rate 20 breaths per min, and tympanic temperature 36.5°C. Scattered crackles were audible in both of lower lungs with no wheezing. Muscle strength of upper limb and lower limb was graded as level 5. Bilateral Babinski’s sign was negative. Rest of physical examination did not reveal any abnormality. Laboratory investigations showed total bilirubin of 7.3 μmol/L (normal range, 1.7–25 μmol/L), alanine aminotransferase of 15 U/L (normal range, 8–40 U/L), aspartate aminotransferase of 22 U/L (normal range, 8–40 U/L), serum urea nitrogen of 7.6 mmol/L (normal range, 1.7–7.1 mmol/L), serum creatinine of 98.3 μmol/L (normal range, 44–133 μmol/L), and C-reactive
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protein (CRP) of 98.9 mg/L (normal range, 0–3.3 mg/L). Creatinine clearance calculated using Cockcroft-Gault equation was 39.1 mL/min (normal range, 80–120 mL/min). A complete blood cell count revealed a platelet count of 225 × 10^3/L (normal range, 100–300 × 10^3/L), and a white blood cells count of 7.3 × 10^3/L (normal range, 4–10 × 10^3/L), with neutrophils percentage of 67.1% (normal range, 46.5–76.5%). Computed tomography (CT) thorax suggested infection with peripheral soft tissue abscess in 3–5 thoracic vertebral body, involving the spinal canal and causing spinal cord compression and a pathological compression fracture of fourth vertebra thoracalis. Lung CT and lung-enhanced CT scan revealed high-density shadow of spotted strip in a different shape with obscure boundaries in upper and lower lobes of both lung with pleural thickening and encapsulated effusion on the left side, and multiple bone (right scapula, sternum midpiece, 3–5 thoracic vertebra) destruction. Abdominal ultrasound detected accessory spleen, two renal cortical cysts, and prostate calcification. Patient received intravenous cefepime 2 g q12h for pulmonary infection after he was admitted to the respiratory ward. Other medications administered included intravenous mannitol (125 mL q8h), oral alendronate sodium (70 mg once weekly), and loxoprofen (60 mg twice daily). However, patient did not improve and on day 9, he had more pain in the right chest with raised CRP (156.9 mg/L). Loxoprofen was changed to intramuscular tramadol (0.1 g qd). One year ago, patient suffered from disseminated histoplasmosis diagnosed with biopsy from the right lung and right scapula. Since patient was not improving with cefepime, on day 12, cefepime was switched to amphotericin B liposome for suspected histoplasmosis (10 mg on 1st day, 15 mg on day 2, 30 mg on day 3, 60 mg on day 4, 120 mg on day 5, and 150 mg on day 6). Patient showed an improvement with relief in pain and decrease in CRP (32.1 mg/L on day 15). However, on day 19, patient developed pain and cyanosis on the right lower limb and both upper limbs as shown in Figures 1 and 2. On day 20, CRP increased to 158.7 mg/L, and on day 23, patient had pain and acrocyanosis with the rise of serum creatinine 147.7 μmol/L. At this, amphotericin B liposome was discontinued, and anisodamine was administered intravenously (20 mg q6 h) for acrocyanosis and pain. After treatment with anisodamine for 9 days, patient showed clinical improvement, CRP decreased to 41.6 mg/L, and serum creatinine was 116.3 μmol/L. On day 29, patient was discharged with a complete cure of acrocyanosis and pain and was prescribed oral voriconazole.

**Figure 1:** Cyanosis at patient’s hand

Causality assessment of the adverse drug reaction (ADR) was carried out using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria and Naranjo’s Scale. In the present case, acrocyanosis and pain improved on withdrawal of amphotericin B liposome and treatment with anisodamine. Thus, ADR was probably caused by amphotericin B liposome (WHO-UMC criteria: Probable; Naranjo’s Score: 5, probable) since there were no other factors that could have caused this ADR. Amphotericin B liposome was discontinued, and anisodamine was used to treat acrocyanosis and pain induced by amphotericin B liposome, so the reaction was a severe ADR with a severity level 3 according to Modified Hartwig and Siegel scale.

**Discussion**

In the present case, acrocyanosis and pain appeared after treatment with amphotericin B liposome and improved when amphotericin B liposome was discontinued. Naranjo ADR probability scale score was 5, the WHO-UMC criteria: Probable, indicating a probable relationship between acrocyanosis and amphotericin B liposome use. Amphotericin B liposome-related acrocyanosis and pain are rare. Acrocyanosis and pain can result from spasm of peripheral vessels and intravenous anisodamine which relieves spasm of smooth muscle was effective to relieve pain and acrocyanosis in the present case. Spasm of peripheral vessels mediated by thromboxane A2 could be responsible for the cyanotic phenomenon and nephrotoxicity by the amphotericin B. Raynaud’s phenomenon is characterized by three-phase reaction, i.e., white, purple, and red precipitated by cold and emotional stress. However, in the present case, only redness and pain were observed, which was different from Raynaud’s phenomenon.

Our patient had impaired renal function (decreased Ccr 39.2 mL/min) with increased age. Patient did not receive concomitant β-receptor blockers, which have been reported to potentiate the likelihood of Raynaud’s symptoms but received mannitol which affects renal function. Amphotericin B-related cyanotic Raynaud’s phenomenon has been reported by Zernikow et al. and Ozaras et al. In the report by Zernikow et al., two young girls and one boy, without impaired renal

**Figure 2:** Cyanosis at patient’s foot
function, developed adverse reaction due to intravenous, or inhalation of conventional amphotericin B, whereas a liposomal preparation was well tolerated. In report by Ozaras et al.,[8] a 50-year-old male developed cyanosis on fingers of hands and feet with amphotericin B deoxycholate and was given amphotericin B lipid complex thereafter without any complication. Patient was undergoing hemodialysis for chronic renal failure.

In the present case, advancing age and impaired renal function could be a possible predisposing factor for amphotericin B liposome-induced elevated serum creatinine because amphotericin B nephrotoxicity is associated with accumulation of the drug in the kidney. Amphotericin B is eliminated by kidney, so potential of accumulation is high in patients with renal impairment and increased age.[10] It was not clear whether amphotericin B liposome-induced acrocyanosis and pain were related with impaired renal function and increased age in the present case. Furthermore, the patient had a history of smoking for about fifty years. Smoking is associated with Raynaud’s phenomenon[11] and Buerger’s disease[12] and impaired peripheral vasculature endothelium-dependent vasorelaxation, which may be considered a risk factor. This report suggests us to pay close attention to the potential risk of amphotericin B-induced acrocyanosis and elevated serum creatinine, especially in elderly patients with impaired renal function and smoking.[11,12]

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**Conflicts of Interest**

There are no conflicts of interest.

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