

Amphotericin B Induced Thrombophlebitis: A Case Report

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ABSTRACT

Amphotericin B is most widely used antifungal drug of choice. We report a case of a 56-year-old man developed pain and skin swelling over right forearm at the intravenous access site during amphotericin B administration treatment given for mucormycosis, the post-operative of sinuses. After 4 hours of affected period, amphotericin B was administration. A well revealed thrombophlebitis of the right forearm was noted. The systemic reaction was assessed based on the naranjo algorithm and was found to be probable. The safety profile of amphotericin B and its adverse effects must be monitored on long term treatment usage.

Key words: Thrombophlebitis, Amphotericin B, Adverse drug reaction,

Pharmacovigilance, Mucormycosis.

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INTRODUCTION

Thrombophlebitis is an inflammatory condition of the vein that leads to erythema, edema, and hardening with pain involving blocking of the superficial veins due to clotting. Thrombophlebitis usually occurs by taking following drugs such as antibiotics, hypertonic dextrose solutions (>10%), cancer chemotherapies, vasoactive medications, solutions containing calcium and potassium supplements.¹ Amphotericin B which is an antifungal antibiotic produced by *Streptomyces nodosus*, binds to ergosterol, an essential component of the fungal cell membrane, causing cell rupture, and eventually causing cell death of the fungi showing antifungal activity. Amphotericin B commonly causes the side effects of nausea, vomiting, rigors, fever, hypertension or hypotension, and hypoxia. The chronic adverse effect causes nephrotoxicity.² However, we observed a patient with skin swelling over right forearm at the intravenous (IV) access site of amphotericin B, so it is called superficial thrombophlebitis. Herein, we described skin swelling over right forearm at the IV access site so it is called superficial thrombophlebitis.

CASE PRESENTATION

A 56-year-old male patient was admitted to the general medicine department with complaints of fever and pain in right facial region since 4 days. On admission his previous records revealed that he was a known case of trigeminal neuralgia on and off for six months and on medication with pregabalin 150 mg once daily (OD). He was also diabetic for 10 years and on metformin 500 mg twice daily (BD). No history of allergy was reported by the patient or in his past medical records. On general examination (day 1) he was found to be conscious, oriented, febrile with presence of pallor of lower palpebral conjunctiva and clubbing of the nail beds of both arms. Vital signs on presentation revealed as an elevated temperature of 99.5°F, normal pulse 86 beats per minute, blood pressure 130/90 mm of Hg and respiratory rate 24/ minute with oxygen saturation of 98% on room air.

Ultrasound of abdomen showed no significant impression. Investigations for infections such as hepatitis B, C and HIV were negative. Routine urine

analysis showed the presence of ketone bodies. Computed tomography (CT) scan of the paranasal sinuses revealed circumferential mucosal wall thickening of right maxillary, right ethmoid, right sphenoid and right frontal sinuses with rarefaction of nasal turbinates and ethmoid septum suggestive of sinusitis. The nasal septum was deviated to left with bony spur indenting left inferior turbinate. There was also the presence of polypoidal mucosal thickening in left maxillary sinus. Magnetic resonance imaging (MRI) of the brain demonstrated ill-defined T1 hypointense, T2 heterogenous intensity lesion noted in the right maxillary and right ethmoid sinus, right sphenoidal recess and right osteomeatal complex blocked. Based on the above findings, the diagnosis of right fungal maxillary sinusitis was made.

The patient underwent functional endoscopic sinus surgery (debridement of all sinuses) and was administered injection amphotericin B liposomal 50 mg as post-surgical prophylactic therapy on day 8. Biopsy result of the debris from nasal cavity reported positive for mucor species. After 3 hours of amphotericin B administration, pain and swelling was seen over the right forearm at the IV access site in the superficial basilica and cephalic veins. (Figure 1)

Examination of the affected area revealed blood clot that blocked the superficial veins (surface of the skin) and swelling from forearm to hand, so called superficial thrombophlebitis. On the day following Amphotericin administration (day 9), laboratory results shown elevated levels of serum creatinine, urea and uric acid as 1.4 mg/dl, 56 mg/dl, and 8.3 mg/dl respectively. (Table 1)

After obtaining opinion from the cardiologist, 7500 international unit (IU) / 0.3 ml of heparin was administered subcutaneously BD and the dose of amphotericin B was decreased to 30 mg. On day 10, the reaction failed to relieve despite dose reduction and as a result it was further reduced to 16.5 mg. With pain and swelling still persistent on the succeeding 2 days, amphotericin B and heparin administration was stopped on day 12. The reaction improved on the subsequent days and he was discharged on day 15 with Thrombophob gel (heparin jelly), Tab.

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Figure 1: Swelling, hardened skin and dark blood clot in the right forearm.

Table 1: Renal function tests of the patient during the treatment in hospital.

Renal Function Tests	Day 1	Day 5	Day 9		Day 11	Day 15	Range
Serum creatinine	0.7	0.9	1.4	Amphotericin B Administration Stopped	1.2	0.8	0.5-1.2 mg/dl
Serum urea	21	23	56		53	22	15-40 mg/dl
Blood Urea Nitrogen	10.2	9.8	19		15	10	7.0-20 mg/dl
Uric acid	5.1	4.9	8.3		6.3	4.2	3.0-7.2 mg/dl

Posaconazole 300 mg OD for 7 days. Patient was advised not to take amphotericin B antifungal in the future.

DISCUSSION

Thrombophlebitis is an inflammatory process associated with a thrombus that affects the superficial veins. Symptoms and signs include local pain, itching, tenderness, redness of the skin, and hardening of the surrounding tissue. Injection used (powder, lyophilized, for solution; Amphotericin B deoxycholate) amphotericin B is an antifungal drug that inhibits fungal cell wall synthesis and not to be used in noninvasive fungal infections like oral thrush, vaginal candidiasis and esophageal candidiasis having normal neutrophil counts caused by *Histoplasma*, *Candida* species, *Sporothrix*, *Aspergillus* species.

On IV infusion of amphotericin 27.5 mg OD administration, in a 4-hr period affected area revealed blood clot that blocked the superficial veins (surface of the skin) and swelling from right forearm to hand associated with pain which is the side effect marked in many studies.^{3,4} To reduce the severity and incidence of Infusion-related adverse events, in our patient we administered heparin but it failed to prevent the reaction and similarly in other study also showed that there was no effect of heparin to treat the reaction.⁵ Finally, based on the Naranjo algorithm, the systemic reaction was assessed and a total score of 8 was noted which is indicated a probable reaction.⁶

Immediately after the notice of adverse event, the hematology tests, liver function, renal functions test and, electrolyte tests were conducted as the previous studies recommend a risk of renal toxicity.⁷ Liver function tests showed no abnormality, whereas, renal function tests showed increased level of serum creatinine 1.4 mg/dl (0.5- 1.2 mg/dl) based on that glomerular filtration rate was calculated to be 56 ml/min/1.73m², serum urea 8.3mg/dl (3.0-7.2 mg/dl) a less renal toxicity that was also seen in previous amphotericin safety studies.^{8,9} There was also decreased level of potassium noted in electrolytes report 3.0 mmol/L (3.5-5.0 mmol/L) noted in earlier study.¹⁰

IV administration of Amphotericin B was stopped as soon as the symptoms appeared and then thrombophob gel ointment, T. Posaconazole 300 mg OD for 7 days was prescribed and patient was discharged.

CONCLUSION

In our report thrombophlebitis was an infusion related side effect observed when amphotericin B given as a post-operative prophylactic for mucormycosis infection because of its antifungal activity. We recommend prescribers, nurses and clinical pharmacists from our study to monitor the safety profile of amphotericin B and its infusion related side effects; neutrophils count and renal function tests on long term treatment. Moreover, patients also should be educated and instructed to avoid such antibiotics which causes side effects in the future.

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Patient Consent

Written informed consent was obtained from the patient for publication of photographs in this case report.

CONFLICT OF INTEREST

The author declare no conflict of interest.

ABBREVIATIONS

IV: Intravenous, **OD:** Once daily, **BD:** Twice daily, **CT:** Computed tomography, **MRI:** Magnetic resonance imaging, **IU:** International unit.

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