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Voriconazole-Induced Hepatotoxicity Resolved after Switching to Amphotericin B in *Fusarium dimerum* Central Line-Associated Bloodstream Infection

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Female, 38-year-old
Final Diagnosis: Drug induced liver injury
Symptoms: Fever • abdominal pain • nausea and vomiting • loose stools
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases • General and Internal Medicine • Pharmacology and Pharmacy

Objective: Rare disease

Background: *Fusarium* spp. is a rare cause of opportunistic life-threatening fungal infections. It has a remarkably high resistance profile with few effective antifungal agents, mostly limited to voriconazole and liposomal amphotericin B. Drug-induced liver injury (DILI) by 1 of these 2 antifungal agents further complicates the management of these infections.

Case Report: A 38-year-old woman with short bowel syndrome presented to the hospital with concerns of abdominal pain and loose stools. An abdominal CT was negative for inflammatory or ischemic bowel disease, and there was no evidence of liver disease. She tested positive for SARS-CoV-2 and required transfer to the ICU due to hypotension requiring fluid resuscitation and vasopressors. On day 43 of her admission, the patient developed a low-grade fever, for which she underwent central-line and peripheral-blood cultures that were positive for *Fusarium dimerum*. The central line was removed and i.v. voriconazole was started. After 3 days of treatment, the patient's liver enzymes rose abruptly. Voriconazole was discontinued and replaced with liposomal amphotericin B, and the liver enzymes improved significantly. The patient completed 14 days of therapy and was discharged from the hospital.

Conclusions: This is a case of *F. dimerum* infection followed by DILI from voriconazole treatment. Her infection was resolved after switching to liposomal amphotericin B, with improvement in liver enzymes on day 1 after discontinuing voriconazole. This observation demonstrates that altering antifungal classes may be an appropriate strategy when confronted with DILI.

Keywords: Chemical and Drug Induced Liver Injury • Fusariosis • Liposomal Amphotericin B • Voriconazole

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/932544

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Background

The *Fusarium* species are filamentous ubiquitous fungi that reside on plants and in the soil. Only a few species (eg, *F. solani*, *F. oxysporum*, and *F. moniliforme*) cause opportunistic infections in immunocompromised patients [1]. The spectrum of disease ranges from superficial to disseminated, life-threatening infections, especially in patients with hematological malignancies and neutropenia. Fusariosis may also affect immunocompetent patients when tissue breakdown occurs as a result of trauma or when a foreign body creates an easy portal of entry.

The *Fusarium* species have a remarkably high resistance profile to common antifungal agents and intrinsic resistance to echinocandins, presenting a major challenge in their treatment [1]. Despite advances in antifungal therapy and the introduction of broad-spectrum agents, invasive fusariosis is associated with high mortality rates, reaching up to 80%.

American and European guidelines currently recommend i.v. voriconazole for the treatment of *Fusarium* spp. infections as first-line medication, with amphotericin B being considered as a second-line agent [2,3]. Posaconazole is recommended as salvage therapy in advanced cases. In addition to antifungal therapy, surgical debridement, removal of foreign bodies (eg, venous catheters), and reversal of immunocompromised states are needed to optimize medical treatment.

Voriconazole use is associated with a high incidence of drug-induced liver injury (DILI), ranging from 3.6% to 60%, limiting its use in fusariosis [4-6]. This has complicated the present scarcity of antifungal agents with activity against *Fusarium* spp. In this case report, we discuss a patient with central line-associated bloodstream infection (CLABSI) caused by *Fusarium dimerum* treated with i.v. voriconazole and complicated by probable DILI.

Case Report

Our patient was a 38-year-old woman known to have hypothyroidism and factitious disorder. She had a previous history of open appendectomy in 2011 complicated by enterocutaneous fistulas requiring repeat laparotomies, small bowel resection, and fistulectomy with subsequent development of short bowel syndrome.

She was admitted in 2020 with abdominal pain and loose stool output from her stoma. Abdominal CT was negative for inflammatory or ischemic bowel disease and did not show any evidence of liver disease. She was found to be positive for SARS-CoV-2. Stool cultures, *Clostridioides difficile* PCR, and ova and parasite examination were negative. Serology for hepatitis A, B, C, and D viruses was negative.

The patient was transferred to the ICU on day 10 of admission due to septic shock. She received meropenem empirically for 11 days (day 10 to day 21); urine and blood cultures at the time were negative. Her hospital course was prolonged due to multiple systematic concerns for which the patient required general anesthesia to complete necessary investigations. Due to difficult peripheral venous access, she had a right internal jugular tunneled central line inserted on day 21 under interventional radiology.

On day 30, the patient developed bacteremia with *Klebsiella pneumoniae* (culture from the tunneled line was negative). She received meropenem for 14 days (day 30 to day 43). On completion of her antibiotic course, the patient started to have a low-grade fever. She underwent central-line and peripheral-blood cultures on day 43, which were positive for the growth of *Fusarium dimerum*. Repeated cultures before antifungal therapy initiation confirmed that *Fusarium dimerum* had colonized the central line, and the patient was treated for CLABSI. The tunneled line was removed on day 45. The patient received weight-dosed voriconazole for 3 days (day 48 to day 50).

On day 51, the patient's liver enzymes rose abruptly. The values on day 51 were aspartate aminotransferase (AST): 459 U/L; alanine aminotransferase (ALT): 331 U/L; alkaline phosphatase (ALP): 237 U/L; gamma-glutamyl transferase (GGT): 35 U/L, and total bilirubin: 6.1 µmol/L. The day before, her enzyme levels were AST 35 U/L, ALT 40 U/L, ALP 172 U/L, GGT 20 U/L, and total bilirubin 4.8 µmol/L (**Figure 1**). We could not determine the serum voriconazole level, as the lab test was unavailable in the hospital at the time. Her Naranjo algorithm score was 7, indicating probable DILI due to voriconazole.

Voriconazole was discontinued (no dose received on day 51) and replaced with liposomal amphotericin B at 5 mg/kg/day. Hydrocortisone 50 mg was given in the first 4 days of treatment due to the patient's history of allergy to multiple antibiotics. Liver enzymes improved the day after. The patient continued to receive liposomal amphotericin B for an additional 9 days (day 51 to day 59). She developed hypokalemia, but otherwise tolerated the regimen and was discharged.

Discussion

We describe a case of CLABSI with *F. dimerum* initially treated with voriconazole until the development of DILI. The fungal infection resolved after switching to amphotericin B, which resulted in improvement in liver enzymes. To the best of our knowledge, this is the first reported case of fusariosis treated with voriconazole and complicated by liver injury.

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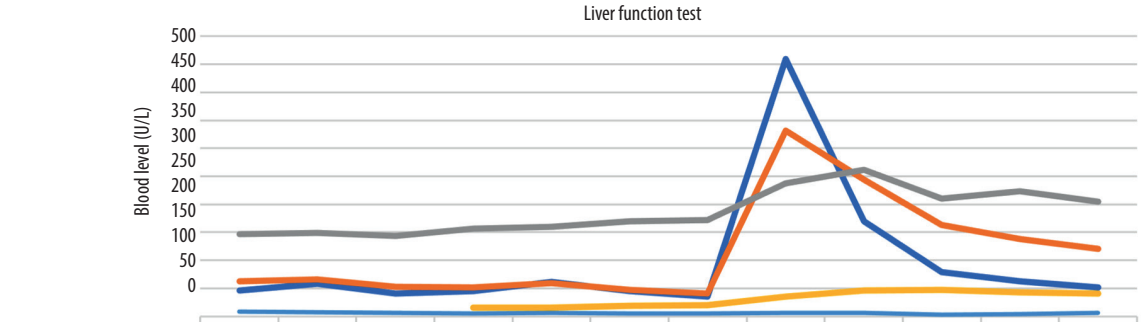

	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
AST	46	58	41	45	61	45	35	459	170	79	62	51
ALT	62	66	52	51	59	47	40	331	244	163	163	120
ALP	147	149	143	156	160	170	172	237	261	210	210	205
GGT				15	15	19	20	35	46	47	47	41
TB (umol/L)	8.3	7.5	5.8	5.4	5.5	4.8	4.8	6.1	5.8	2.8	2.8	6.1

Figure 1. Day 0 represents the initiation of voriconazole. Day 3 represents discontinuation of voriconazole and initiation of liposomal amphotericin B. AST – aspartate aminotransferase (reference range: 5-34 U/L); ALT – alanine aminotransferase (reference range: 5-55 U/L); ALP – alkaline phosphatase (reference range: 40-150); GGT – gamma-glutamyl transferase (reference range: 9-36); TB – total bilirubin (reference range: 3.4-20.5 micromole/L).

DILI refers to hepatic injury caused by drugs metabolized by the liver that can result in disease signs ranging from minor elevation in liver function tests to serious life-threatening hepatitis and hepatic necrosis. The overall incidence of DILI is estimated to be approximately 19 cases per 100 000 persons per year, with 2.9% of these cases caused by antifungal agents [7]. Our patient developed elevated ALT on the third day of voriconazole administration, to 331 U/L (normal range: 5-55 U/L). The magnitude of elevation in AST (6X UNL) and ALT (13.5X UNL) in our case prompted an urgent action to discontinue the most likely offending agent, voriconazole. Based on our evaluation, no other concomitant medications could have contributed to this elevation in liver transaminases or resulted in significant drug-drug interaction with voriconazole. Application of the Naranjo algorithm suggested probable attribution to voriconazole. Fortunately, this significant elevation in liver enzymes improved the next day and did not lead to severe liver damage or failure.

Voriconazole-induced DILI is a dose-dependent toxicity that positively correlates with drug serum concentration [8]. Each 1 µg/mL increase in voriconazole serum concentration is associated with predictable increases in AST, alkaline phosphatase, and total bilirubin of 13.1%, 16.5%, and 17.2%, respectively. However, a specific threshold at which voriconazole causes DILI has not been established. Unfortunately, we were unable to assess the voriconazole serum concentration in our case.

Voriconazole is extensively metabolized by liver cytochrome P450 enzymes to inactive metabolites [9]. It has the ability to interact with other medications that induce or inhibit liver enzymes (eg, CYP2C19, CYP3A4, CYP2C9). Glucocorticoids have been shown in vitro to induce CYP2C19, leading to its upregulation [10]. In one study, dexamethasone use was linked to a 3.75-fold decrease in voriconazole concentration [11]. Likewise, coadministration of dexamethasone and methylprednisolone resulted in 1.65- and 1.93-fold decreases in voriconazole concentration, respectively [12]. Although our patient received pre-medication with hydrocortisone on switching to liposomal amphotericin B, we do not believe its administration explains the rapid improvement in liver enzyme levels, which occurred within one day; the effect of corticosteroids on voriconazole clearance would be expected to take longer. If an immunological response induced the liver injury, pre-medication with hydrocortisone may have contributed to augmenting recovery.

Liposomal amphotericin B has also been demonstrated to cause DILI in multiple case reports [13,14]. When compared to voriconazole, liposomal amphotericin B has a similar incidence of hepatotoxicity when used for empiric therapy in patients with neutropenia and persistent fever, according to a large multicenter trial [15]. However, switching to it in our case led to an instant improvement in liver enzymes and helped maintain an effective antifungal regimen.

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Conclusions

Altering antifungal classes may be an appropriate strategy when confronted with DILI. This becomes of great importance when treating rare fungal infections with limited effective antifungal agents.

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Conflict of Interest

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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