Case Report

Disseminated Fusarium infection in an immunocompromised patient Successful outcome with combined antifungal therapy

PGRUM Welagedara[1], UABP Somawardana[2], NP Madarasinga[3], MAN Manchanayaka[4], CN Wijesinghe[4], GDI. Prematthilaka[1], PGRIS Welagedara[1], LSM Sigera[1], SP Gunasekera[4], PI Jayasekera[1]

Sri Lankan Journal of Infectious Diseases 2022 Vol.12(2):E23 1-6

DOI: http://dx.doi.org/10.4038/sljid.v12i2.8477

Abstract

Fusarium species are plant pathogens which exist ubiquitously in the environment. While they can cause superficial and subcutaneous infections in healthy individuals, they can give rise to deep and disseminated infections in immunocompromised patients, particularly in patients with haematological malignancies with a high risk of mortality. This case describes a young male diagnosed with B Cell Acute Lymphoblastic Leukaemia (B-ALL) who developed disseminated *Fusarium* infection with febrile neutropenia following induction chemotherapy. Necrotic skin lesions led to the diagnosis in this patient. Though the patient had a clinical recurrence of infection due to inadequate treatment initially, he was finally completely cured with combined antifungal therapy using amphotericin B and voriconazole.

Keywords: Fusarium sp., disseminated, immunocompromised

Introduction

The genus *Fusarium* causes a wide range of infections in healthy individuals and disseminated infection in patients with impaired immunity.[1] We present a patient with haematological malignancy who developed invasive fusariosis during the induction phase of chemotherapy. Dermatological manifestations were the key to diagnosis, and he was successfully managed with combined antifungal therapy with amphotericin B and voriconazole.

Case Report

An eighteen-year-old male was diagnosed with B-ALL and presented to the National Cancer Institute of Sri Lanka with fever for one week. He had no detectable focus of infection and was haemodynamically stable. He had pancytopenia with profound neutropenia [absolute

[1]*Department of Mycology, Medical Research Institute, Colombo 8, Sri Lanka*
[2]*Department of Haemato-Oncology and Stem Cell Transplantation, Apeksha Hospital, Maharagama, Sri Lanka*
[3]*Department of Dermatology, Apeksha Hospital, Maharagama, Sri Lanka*
[4]*Department of Microbiology, Apeksha Hospital, Maharagama, Sri Lanka*

Address for correspondence: Dr. PGRUM Welagedara, Department of Mycology, Medical Research Institute, Colombo 8, Sri Lanka. Telephone+94714398741. email: pgrumw@gmail.com

https://orcid.org/0000-0002-2824-0140

Received 24 February 2022 and revised version accepted 27 May 2022. Published on 26 July 2022

neutrophil count (ANC) 48/µL]. His C-reactive protein (CRP) was elevated (308.6 mg/L) but blood culture remained sterile. He was started on IV piperacillin tazobactam, amikacin and metronidazole. Oral acyclovir and fluconazole were started prophylactically.

As the fever settled with treatment, phase I induction chemotherapy was started. From the next day onwards, he developed intermittent high fever spikes and neutropenia further worsened. Antibiotics were upgraded to meropenem, and fluconazole was changed to voriconazole. After 3 days of chemotherapy, he developed periorbital cellulitis. IV clindamycin and liposomal amphotericin B were commenced and voriconazole was omitted.

On day 10 of starting chemotherapy, he developed painful erythematous skin lesions over the limbs. They gradually turned to blisters and ruptured to leave ulcers with necrotic centres (Figure 1) and the patient continued to be febrile with no other systemic symptoms.

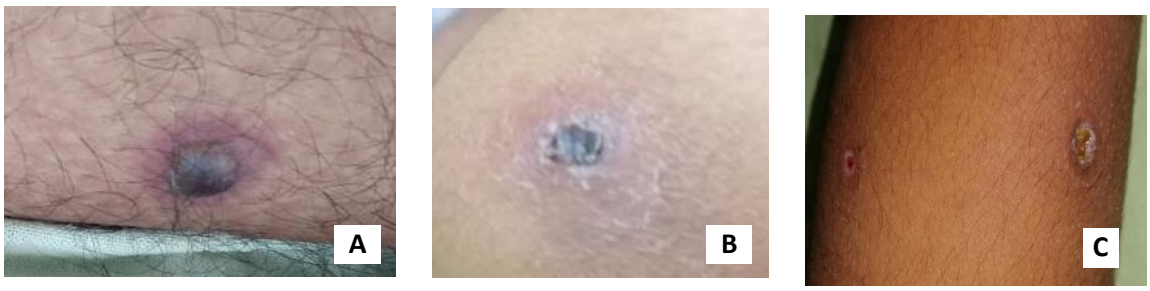


Figure 1: Cutaneous lesions of the patient: A: haemorrhagic blister. B: erythematous macule with central necrosis. C: ulcer

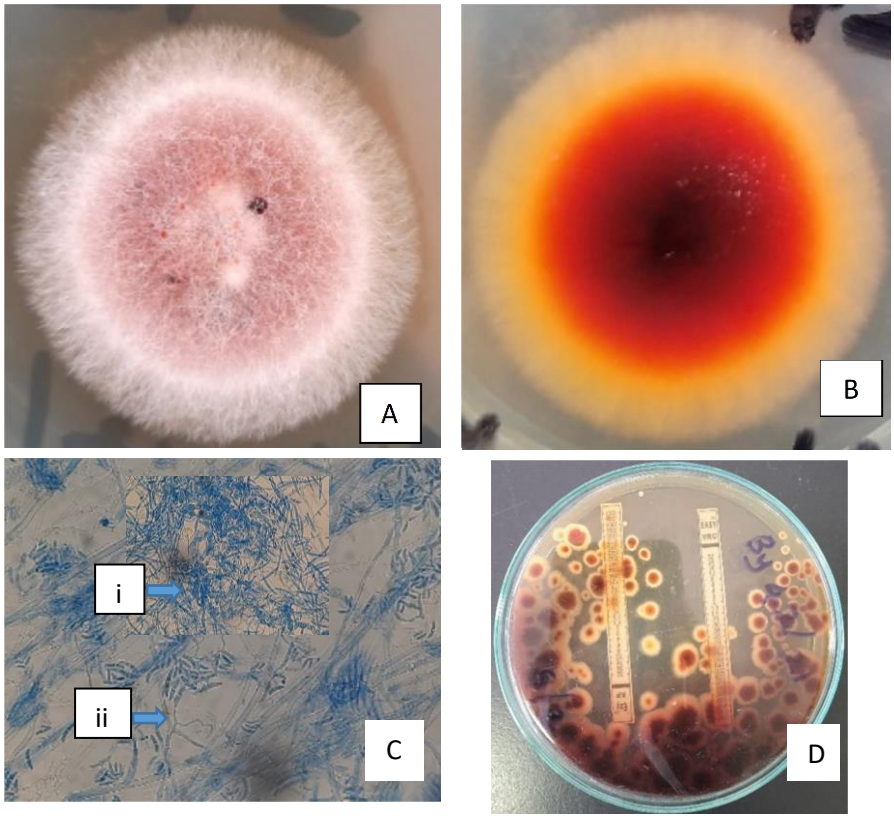
Oral acyclovir was changed to IV acyclovir suspecting *varicella* infection. Chemotherapy was withheld and dermatology opinion was sought. A skin biopsy was performed suspecting a fungal infection or a drug reaction. Meanwhile liposomal amphotericin B was omitted after completing 17 days of treatment.

Bacterial cultures of the skin biopsy and the fungal blood culture remained sterile. The biopsy specimen was inoculated onto Sabouraud Dextrose Agar (SDA) and incubated at 26 ^{o}C and 37 ^{o}C at the Mycology Reference Laboratory. Fungal filaments were seen in the 10% KOH direct smear made from the rest of the specimen. A white floccose growth was noted after 5 days incubation which gradually became tinged with purple. The isolate was finally identified as a *Fusarium* species with lactophenol cotton-blue mount. The macroscopic and microscopic morphological features were not compatible with the available key of the mycology atlas. In the absence of molecular diagnostic methods, speciation was not possible. Minimum Inhibitory Concentration (MIC) of voriconazole, and amphotericin B determined on Roswell Park Memorial Institute agar (RPMI) were 0.5µg/ml and 2µg/ml respectively (Figure 2). Break points are not well established for most of the moulds, including fusarium. Only the epidemiological cut off values (ECV) are given for some species.[2] According to CLSI, ECV for non-dermatophyte filamentous fungi is 1µg/ml.[3]

The patient was started on IV voriconazole 200mg 12 hourly following a loading dose of 400mg 12 hourly for 1 day. Since the patient was clinically responding to antifungal therapy, chemotherapy was restarted, IV voriconazole was omitted after seven days and the patient was discharged home following blood count recovery upon completion of induction chemotherapy

on oral voriconazole. Neutropenia lasted nearly 1 month during this admission. The patient was readmitted for the standard BFM consolidation chemotherapy after two weeks of completion of induction chemotherapy.

During the neutropenic phase following chemotherapy, he developed fever and pain in the right ear with a serous discharge from the ear. CT brain showed right sided mastoiditis with no abscess formation or intracranial infiltration. He was continued on IV meropenem, vancomycin, amikacin with liposomal amphotericin B. Meanwhile, a sinus tract was noted over the nose with nasal deformity. Recurrence of *Fusarium* infection was suspected clinically. No cultures were sent. A few healing cutaneous lesions were also noted (Figure 3).



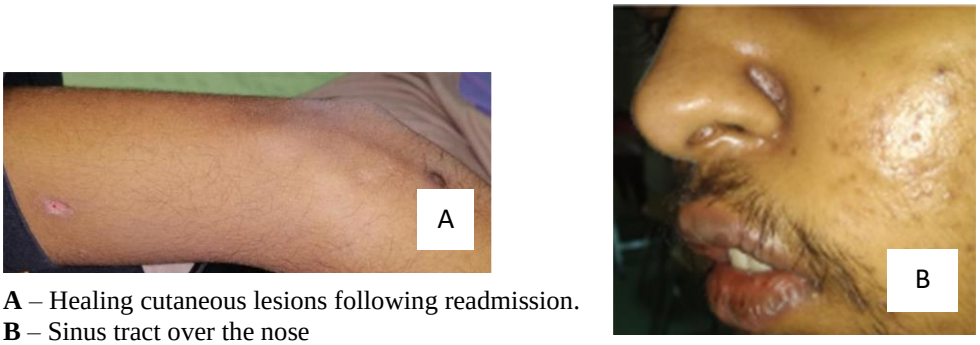
A: Obverse view of colony on SDA after 5 days (fast growing) of incubation at 26 ^{o}C; Floccose, white to peach colony becoming tinged with purple.

B:Reverse view of colony on SDA after 5 days of incubation at 26 ^{o}C; brownish red pigmented colony

C:Slide culture microscopic appearance of the isolate; Abundant sickle shaped macro conidia with 3-5 septa, sparse micro conidia with presence of chlamydospores (i) and poly phialides (ii).

D:AFST performed on RPMI agar demonstrating MIC values of 2 µg/l for amphotericin B and 0.5 µg/l for voriconazole.

Figure 2: Culture appearance and AST

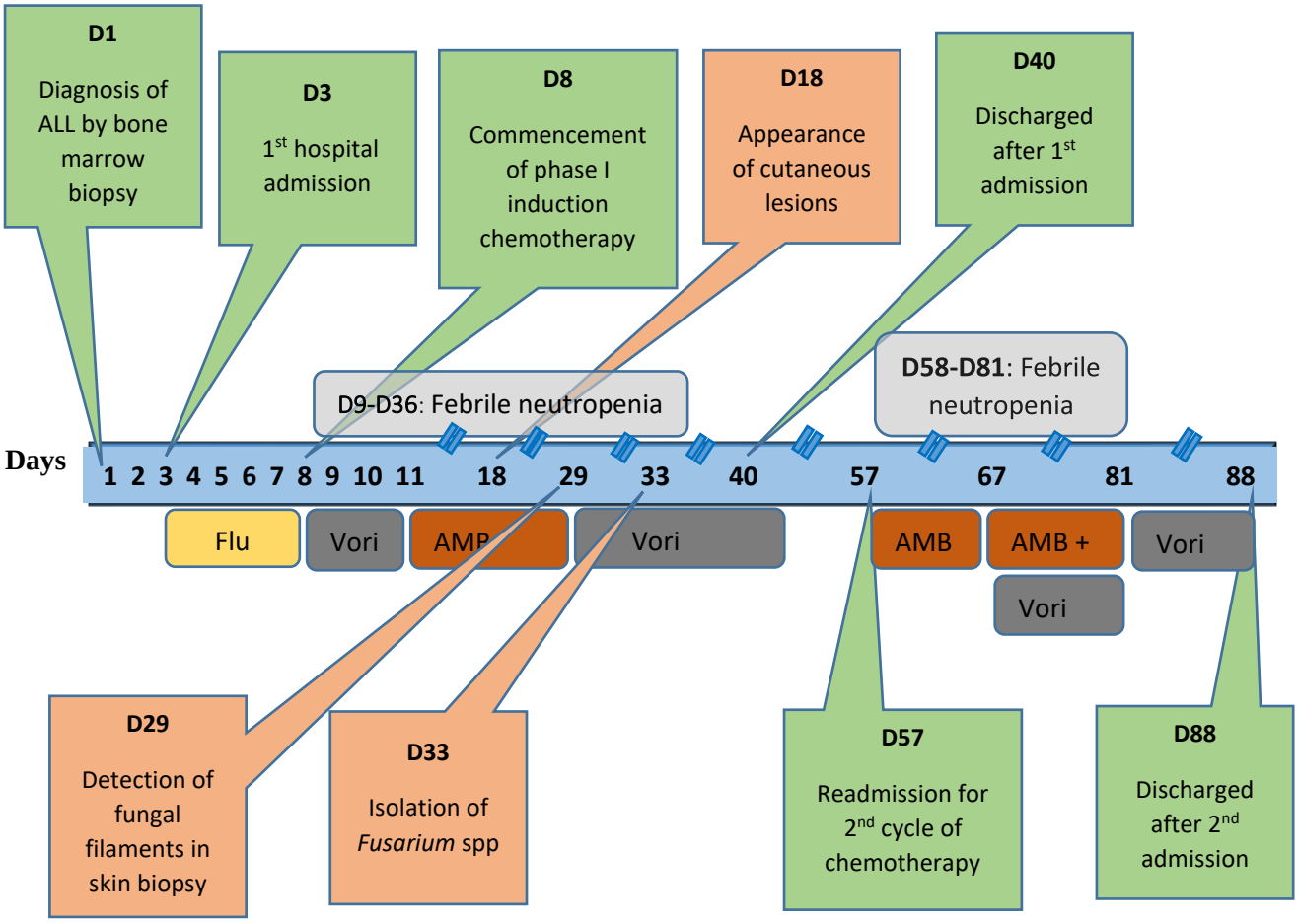


A – Healing cutaneous lesions following readmission.
B – Sinus tract over the nose

Figure 3: Lesions seen during readmission

A combination of oral voriconazole and IV liposomal amphotericin B were started. His fever gradually subsided and he was able to complete the consolidation chemotherapy successfully. The patient was discharged from the hospital upon blood count recovery following completion of chemotherapy after one month of the 2nd hospital admission. He completed a course of IV liposomal amphotericin B for 2 weeks and oral voriconazole for 3 weeks prior to discharge.

The timeline of the clinical course is shown in Figure 4



- **Fluconazole** (Flu): [D3-D8]
- **Voriconazole** (Vori): [D8-D11], [D29-D47], [D81-D88]
- **Amphotericin B** (AMB): [D11-D29], [D58-D67]
- **Amphotericin B + Voriconazole**: [D67-D81]

Figure 4: Time line of clinical course including antimicrobial treatment

Discussion

Fusarium species are the second commonest moulds causing fungal infections in the immunocompromised population, particularly those with haematological malignancies.[4,5] Refractory fever is the commonest manifestation of disseminated fusariosis in more than 90% of patients, followed by cutaneous lesions and sino-pulmonary infections (~75%).[4] This case

describes a patient with acute leukaemia who developed refractory intermittent fever not responding to broad spectrum IV antibiotics during prolonged severe neutropenia. He developed necrotic skin lesions characteristic of disseminated fusariosis.

Cutaneous features of disseminated fusariosis can range from erythematous macules, subcutaneous nodules, blisters, targetoid lesions and necrotic ulcers. In 50% of patients, the diagnosis is made by cutaneous lesions similar to those seen in this case. Though blood culture positivity rate (40%) is higher in fusariosis than aspergillosis, it was negative in this case.[4] Therefore, any suspicious cutaneous lesions should be biopsied and investigated since it could be the only clinical manifestation.[5]

Treatment with appropriate antifungal drugs is important in immunocompromised patients with disseminated *Fusarium* infection due to the high mortality rate (50-80%).[4,6] ESCMID and ECMM joint guidelines recommend voriconazole and liposomal amphotericin B as first line treatment options in immunocompromised patients with strong and moderate strength respectively.[7] However, amphotericin B and voriconazole combination have shown synergism in some other studies resulting better outcome in patients.[8–10]

The *Fusarium* culture isolate of this patient had a higher MIC for amphotericin B than for voriconazole. Our patient had a favourable outcome with prolonged treatment with both antifungals. Speciation was not possible due to unavailability of molecular methods for identification, and we were therefore unable to compare the MIC values with available epidemiological cut off values.[2]

Other than the treatment with antifungal drugs, reversal of immunosuppression and surgical debridement of infected tissue are highly recommended in optimizing the outcome of patients with disseminated *Fusarium* infection. [7]

Conclusion

Disseminated Fusarium infection is an emerging life-threatening disease in immunocompromised patients. Early clinical suspicion and diagnosis is necessary to commence on appropriate antifungal therapy, to achieve an optimum outcome in susceptible patients. Combined antifungal therapy is effective in disseminated fusariosis when inadequate response is achieved with monotherapy.

Declarations

Acknowledgement: None
Funding source: None
Conflict of Interest: Authors declare that there are no conflicts of interest.
Ethics statement: Consent for publication was obtained from the patient.
Author contributions: All authors have contributed. All were involved in the diagnosis and management of the patient. PGRUMW wrote the manuscript. PIJ, UABPS, NPM, and SPG: supervised the manuscript writing.

References

1. Van Diepeningen AD, Brankovics B, Iltes J et al. Diagnosis of *Fusarium* infections: approaches to identification by the clinical mycology laboratory. *Curr fungal infect rep.* 2015; 9(3):135–43. *doi: https://doi.org/10.1007/s12281-015-0225-2*
2. Espinel-Ingroff A, Colombo AL, Cordoba S et al. International evaluation of MIC distributions and epidemiological cut-off value (ECV) definitions for *Fusarium* species identified by molecular methods for the CLSI broth microdilution method. *Antimicrob Agents Chemother*. 2016; 60(2):1079–84. *doi: https://doi.org/10.1128/AAC.02456-15*
3. CLSI. *Method for antifungal disk diffusion susceptibility testing of nondermatophyte filamentous fungi; approved guideline*. CLSI document M51-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2010. *No doi*
4. Dignani MC, Anaissie E. Human fusariosis. *Clinical Microbiology and Infection*. 2004; 10:67–75. *doi: https://doi.org/10.1111/j.1470-9465.2004.00845.x*
5. Maddy AJ, Sanchez N, Shukla BS et al. Dermatological manifestations of fungal infection in patients with febrile neutropaenia: a review of the literature. *Mycoses.* 2019; 62(9):826-834 *doi: https://doi.org/10.1111/myc.12928*
6. Yu J, Chen Y, Fang J et al. Successful treatment of disseminated fusariosis in a patient with acute lymphoblastic leukemia. *Medicine* (Baltimore) *doi: https://doi.org/10.1097/MD.0000000000016246*
7. Tortorano AM, Richardson M, Roilides E et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others. *Clinical microbiology and infection*. 2014; 20:27–46. *doi: https://doi.org/10.1111/1469-0691.12465*
8. Martin-Vicente A, Guarro J, Capilla J. Does a triple combination have better activity than double combinations against multiresistant fungi? experimental in vitro evaluation. *International Journal of Antimicrobial Agents*. 2017; 49(4):422–6. *doi: https://doi.org/10.1016/j.ijantimicag.2016.12.015*
9. Ruíz-Cendoya M, Pastor J, Guarro J. Combined therapy against murine-disseminated infection by *Fusarium verticillioides*. *Mycopathologia*. 2011; 171(3):171–5. *doi: https://doi.org/10.1007/s11046-010-9364-8*
10. Ho DY, Lee JD, Rosso F et al. Treating disseminated fusariosis: amphotericin B, voriconazole or both? *Mycoses*. 2007; 50(3):227–31. *doi:https://doi.org/ 10.1111/j.1439-0507.2006.01346.x*