Clin. Lab. 2025;71:XXX-XXX

CASE REPORT

Fusarium Fungemia of T-lymphoblastic Lymphoma after HSCT: a Case Report and Review of the Literature

Tianqi Qi [1], Qian Liu [1], Xinyue Liu [3], Qi Hao [3], Fuwei Wu [1], Chang Liu [2]

[1] *Department of Clinical Laboratory, Aerospace Center Hospital, Beijing, P. R. China*
[2] *Department of Clinical Laboratory, The First Affiliated Hospital of Tsinghua University, Beijing, P. R. China*
[3] *Department of Hematology Laboratory, Aerospace Center Hospital, Beijing, P. R. China*

SUMMARY

***Background:* *Fusarium* species is a facultative pathogen capable of causing invasive infections in patients with hematological malignancies after allogeneic hematopoietic stem cell transplantation (HSCT).**
***Methods:* We retrospectively analyzed a case of T-lymphoblastic lymphoma combined with disseminated fusariosis after HSCT in our hospital. Case reports of *Fusarium* fungemia in patients with hematological disorders over the past 20 years in Asia were reviewed.**
***Results:* Despite undergoing treatment with a combination of amphotericin B and voriconazole, the patient ultimately succumbed to multiple organ failure.**
***Conclusions:* *Fusarium* fungemia poses a fatal outcome. The adequate courses of antifungal medications are crucial.**
(Clin. Lab. 2025;71:xx-xx. DOI: 10.7754/Clin.Lab.2024.240836)

Correspondence:
Chang Liu
Department of Clinical Laboratory
The First Affiliated Hospital of Tsinghua University
Beijing
P. R. China
Email: liuchang_xtn@163.com

Fuwei Wu
Department of Clinical Laboratory
Aerospace Center Hospital
Beijing
P. R. China
Email: 564245665@qq.com

Case Report accepted September 2, 2024

KEYWORDS

Fusarium, fungemia, hematologic malignancies, antifungal therapy

INTRODUCTION

Fusarium species were initially discovered in 1958 [1], and the first case of *Fusarium* bloodstream infection was reported in 1973, demonstrating that *Fusarium* spp. could infect a human host [2]. *Fusarium* spp. is a facultative pathogen capable of causing invasive infections in patients with hematological disorders and immune deficiencies. T-lymphoblastic lymphoma (T-LBL) is a highly aggressive tumor originating from immature precursor T lymphocytes [3]. The annual incidence ranges from 1 to 5 per 100,000 adults and is higher in Asia compared to Europe and the United States. This study reports a case of *Fusarium* bloodstream infection in a patient with T-LBL after allogeneic hematopoietic stem cell transplantation (HSCT), offering a reference for future clinical treatment.

Table 1. The minimal inhibitory concentrations (MIC) of antifungal agents against FSSC.

Antifungals	MIC in this case (μg/mL)	MICs in previous reference [24]			
		Method	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
Amphotericin B	2	CLSI	≤ 0.25 to 16	-	-
Itraconazole	> 16	CLSI	0.5 to ≥ 16	-	-
Posaconazole	> 8	CLSI	1 to ≥ 16	-	-
Voriconazole	4	CLSI	0.5 to ≥ 16	-	-
Isavuconazole	-	EUCAST	4 to ≥ 16	> 16	> 16
Olorofim	-	CLSI	1 to > 4	> 4	> 4
Manogepix	-	CLSI	≤ 0.015 *	-	-

FSSC - *Fusarium solani* species complex, MIC - minimum inhibitory concentration, CLSI - Clinical and Laboratory Standard Institute, EUCAST - European Committee on Antimicrobial Susceptibility Testing, * - minimal effective concentration.

CASE PRESENTATION

A 19-year-old male (61.5kg) visited a local physician in August 2023 with progressive enlargement of the left cervical lymph nodes accompanied by fever. Lymph node biopsy and bone marrow cytology were performed, and the patient was finally diagnosed as T-LBL. He was treated with chemotherapy regimens at local hospitals, but there was an unsatisfactory response with multiple extramedullary lesions developing. The mouse-derived chimeric antigen receptor T-cell (CAR-T) cells were infused on December 2023 and the bone marrow smears showed complete remission. The patient was admitted to our hospital for transplantation, and the donor was his father (HLA high-resolution 7/10, O supplied B). After pretreatment scheme, the patient was infused with related haploid peripheral blood hematopoietic stem cells (274 mL; TNC 9.78 x 10^8/kg, MNC 6.55 x 10^8/kg, CD34+ 4.3 x 10^6/kg) on February 18, 2024. Sore throat and scrotal pain appeared, accompanied by elevated temperature to 37.5℃ at + 1 day after reinfusion (absolute neutrophil count [ANC]: 0.55 x 10^9/L). Multiple dark purple nodules visible on scrotal skin with tenderness but no significant abnormalities of male ultrasound at + 3 day. The temperature elevated over 38.0℃ for the first time and agranulocytosis (ANC: 0.08 x 10^9/L) persisted. Blood culture (peripherally inserted central catheter and peripheral blood) showed *Fusarium* infection at + 5 day. The result of 1,3-beta-D-glucan (Dynamiker, Tianjin, China) increased to 103.18 pg/mL within one week, but consistently negative galactomannan (GM) results. During hospitalization, the temperature changes, time to positivity and infection indicators (C-reactive protein and procalcitonin) are shown in Figure 1.

The patient's blood culture specimen was subjected to Gram staining (Figure 2A, B) and fluorescence staining (Figure 2C, D). The microscopic examination of a smear revealed oval, kidney-shaped, or peanut-shaped spores, as well as septate hyphae, suggestive for *Fusarium* spp. and confirmed with culture. Macroscopically, the culture on Sabouraud agar incubated at 28℃ for 5 days grew a velvety surface that was grayish-white on the front and yellow-brown on the back (Figure 2E, F). VITEK® MS (BioMerieux, Lyon, France) identified the spectra matching the level of *Fusarium solani* species complex (FSSC). The Sensititre® YeastOne™ colorimetric method was used for the antifungal susceptibility test (Table 1).

The initial regimens were liposomal amphotericin B (L-AMB) 5 mg/kg/d and voriconazole (VRC) 200 mg q12h. Considering the progression of patient's skin nodules, we added caspofungin (CPFG) 50 mg qd and granulocyte transfusions from healthy donors at + 8 day. Due to the progressive level of creatinine, the AMB was switched to topical application. VRC was escalated to 400 mg q12h combined with isavuconazole 200 mg q12h and micafungin (MCF) 100 mg qd at + 11 day. To remove increased inflammatory mediators, continuous renal replacement therapy (CRRT) was supported at + 12 day. Due to continued blood culture positivity, the treatment finally switched to L-AMB (300 mg qd), VRC (400 mg q12h), and MCF (300 mg qd) at + 14 day. The trough concentrations of VRC were monitored through fungal treatment phase (Figure 1).

Review of the Literature

We reviewed previous cases of hematologic disease with fusarium bloodstream infection from PubMed databases from 2004 to 2024 in Asia. We excluded cases from non-Asian regions, cases of disseminated Fusarium infection without bloodstream infection, and cases with incomplete clinical data, and finally selected a total of 19 cases (Table 2) [4-20]. Of the 20 patients (one case is our study), *Fusarium* spp. identified were *F. solani* (10 cases), *F. fujikuroi* (3 cases), *F. keratoplasticum* (1 case), *F. oxysporum* (1 case), and five cases categorized only as *Fusarium* spp. Sixteen cases were confirmed by two or more methods, including polymerase chain reaction (5 cases), internal transcribed spacer (4

Table 2. Literature review of hematologic disease with fusarium bloodstream infection in Asia (2004 - 2024).

Clinical manifestation	Other sites of infection	Antifungal therapy	Outcome
multiple skin lesions, multiple nodules, meningospondylodiscitis	skin, brain, lung, liver, spleen, kidney	L-AMB	died
fever, multiple skin lesions abscesses, visual loss	skin, soft tissue, eye, kidney	D-AMB, VRC	survived
fever, multiple skin lesions, multiple nodules	skin, soft tissue, lung	FCA, D-AMB, VRC	survived
fever, multiple skin lesions, visual loss	skin, eye	ANF, L-AMB, VRC	survived
fever, multiple skin lesions, visual loss, myalgia	skin, soft tissue, eye	L-AMB, ITC, VRC	died
fever, multiple skin lesions, abscesses	skin, soft tissue	VRC, L-AMB, CPFG	died
fever, multiple skin lesions	skin, soft tissue	ITC, L-AMB, VRC	survived
fever, multiple skin lesions	skin	L-AMB	died
fever, multiple skin lesions	skin	VRC, L-AMB	died
fever, multiple skin lesions, multiple nodules	skin, lung	L-AMB, VRC	survived
fever, multiple skin lesions, abscesses	skin, soft tissue	L-AMB	survived
fever, multiple skin lesions	skin	ITC, L-AMB, VRC, CPFG	died
fever, multiple skin lesions	skin, soft tissue	FCA, L-AMB, VRC	survived
fever, multiple skin lesions, myalgia, sinusitis	skin, soft tissue, nose	PSC, CPFG, VRC, L-AMB	survived
fever, multiple skin lesions, multiple nodules, meningospondylodiscitis	skin, joints, soft tissue, liver, spleen, brain	VRC, PSC, L-AMB	died
fever, multiple skin lesions	skin	D-AMB, VRC, PSC	survived
multiple skin lesions	skin	L-AMB, ITC	survived
multiple skin lesions	skin	L-AMB, VRC	died
multiple skin lesions	skin	L-AMB	died
fever, multiple skin lesions	skin	L-AMB, VRC, CPFG, MCF, ISA	died

Table 2. Literature review of hematologic disease with fusarium bloodstream infection in Asia (2004 - 2024) (continued).

Age (years) /gender	Hematologic disease	Trans-plantation	Fusarium species	Author [reference] /published year	Method of identification
58/F	AML	NA	*F. fujikuroi*	Yun SJ, et al. [4]/2007	pathological, blood and tissue culture, PCR
9/M	ALL	NA	*Fusarium* spp.	Kah TA, et al. [5]/2011	pathological, BC
27/M	CTCL	NA	*F. solani*	Liu JY, et al. [6]/2011	pathological, BC ITS
49/F	ALL	NA	*F. solani*	Fan F, et al. [7]2012	BC
21/M	SAA	HSCT	*F. solani*	Cheng P, et al. [8]/2014	BC, PCR
22/M	AA	HSCT	*Fusarium* spp.	Das K, et al. [9]/2015	BC
24/F	AML	NA	*F. kerato-plasticum*	Chiewchanvit S, et al. [10]/2017	pathological, BC, MLST
70/M	ALL	NA	*Fusarium* spp.	Kurosawa S, et al. [11]/2017	BC
44/M	SAA	CBT	*F. solani*	Okada K, et al. [12]/2018	BC, PCR, ITS
31/F	ALL	NA	*F. solani*	Yu J, et al. [13]/2019	pathological, BC, ITS
46/M	MPAL	NA	*F. solani*	Ang A, et al. [14]/2020	pathological, BC, sanger-sequencing
53/M	AML	HSCT	*F. fujikuroi*	Fujishita K, et al. [15]/2020	pathological, BC
13/F	AML	NA	*F. solani*	Ning JJ, et al. [16]/2021	pathological, BC
13/M	AML	NA	*F. solani*	Lin ZL, et al. [17]/2022	BC, mNGS
14/M	ALL	NA	*Fusarium* spp.	Fei H, et al. [18]/2022	pathological, BC, pus cell culture
15/F	ALL	NA	*F. fujikuroi*	Zhong L, et al. [19]/2022	pathological, blood culture and tissue culture, PCR, ITS
13/M	AML	NA	*F. oxysporum*	Kim JY, et al. [20]/2023	BC
30/M	ALL	NA	*Fusarium* spp.	Kim JY, et al. [20]/2023	pathological, BC
54/F	AML	NA	*F. solani*	Kim JY, et al. [20]/2023	pathological, BC, PCR
19/M	T-LBL	HSCT	*F. solani*	This case	BC, mNGS

Table 2. Literature review of hematologic disease with fusarium bloodstream infection in Asia (2004 - 2024) (continued).

Country	Korea	Malaysia	Taiwan, China	Hong Kong, China	China	India	Thailand	Japan	Japan	China	Singapore	Japan	China	China	China	China	Korea	Korea	Korea	China
Author [reference] /published year	Yun SJ, et al. [4]/2007	Kah TA, et al. [5]/2011	Liu JY, et al. [6]/2011	Fan F, et al. [7]2012	Cheng P, et al. [8]/2014	Das K, et al. [9]/2015	Chiewchanvit S, et al. [10]/2017	Kurosawa S, et al. [11]/2017	Okada K, et al. [12]/2018	Yu J, et al. [13]/2019	Ang A, et al. [14]/2020	Fujishita K, et al. [15]/2020	Ning JJ, et al. [16]/2021	Lin ZL, et al. [17]/2022	Fei H, et al. [18]/2022	Zhong L, et al. [19]/2022	Kim JY, et al. [20]/2023	Kim JY, et al. [20]/2023	Kim JY, et al. [20]/2023	This case

M - male, F - female, AML - acute myelocytic leukemia, ALL - acute lymphocytic leukemia, AA - aplastic anemia, SAA - severe aplastic anemia, MPAL - mixed phenotype acute leukemia, CTCL - cutaneous t-cell lymphoma, T-LBL - T-lymphoblastic lymphoma, NA - not applicable, CBT - cord blood transplantation, HSCT - hematopoietic stem cell transplantation, BC - blood culture, PCR - polymerase chain reaction, ITS - internal transcribed spacer, mNGS - metagenomic next-generation sequencing, MLST - multilocus sequencing typing, L-AMB - liposomal amphotericin B, ITC - itraconazole, VRC - voriconazole, D-AMB - amphotericin B deoxycholate, FCA - fluconazole, ANF - anidulafungin, CPFG - caspofungin, PSC - posaconazole, MCF - micafungin, ISA - isavuconazole.

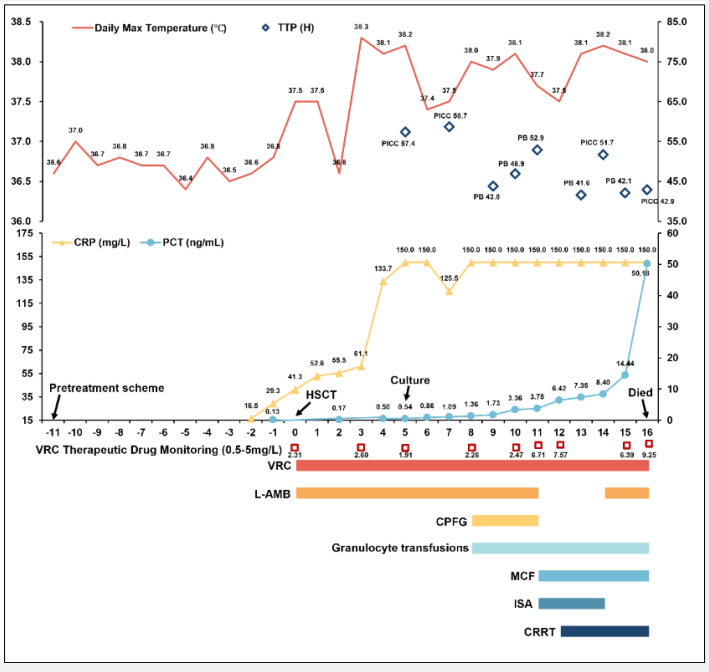

Figure 1. Clinical course of our case with time to positivity (TTP, hours), daily max temperature, C-reactive protein (CRP, upper limit of detection: 150 mg/L), procalcitonin (PCT), antifungal treatment (L-AMB - liposomal amphotericin B, VRC – voriconazole, CPFG - caspofungin, ISA - isavuconazole, MCF - micafungin) and supportive treatment (CRRT, continuous renal replacement therapy).

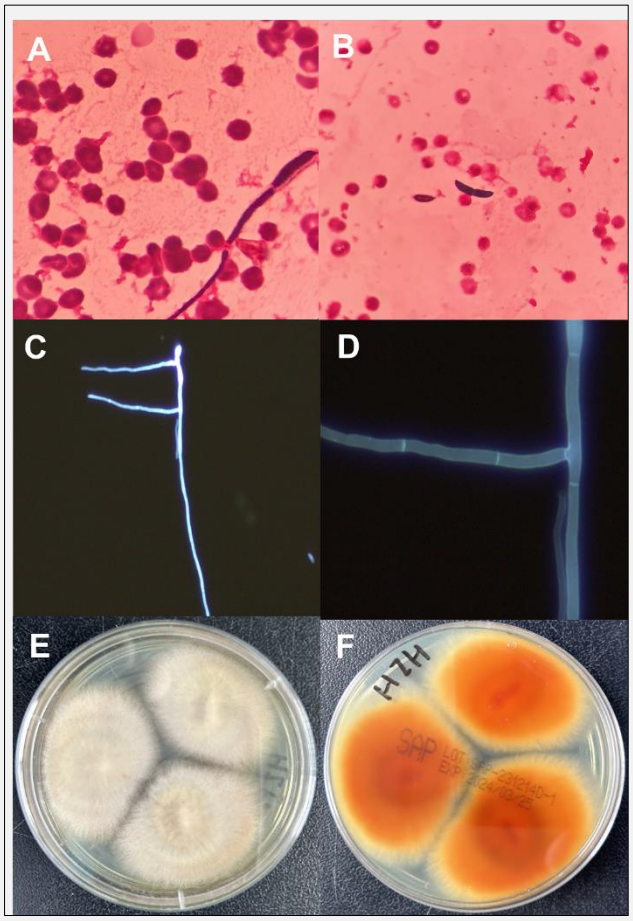

Figure 2. *Fusarium solani* from the blood culture. A, B) Microscopic image of Fusarium stained with Gram staining under 1,000 x magnification. C, D) Microscopic image of Fusarium stained with fluorescence staining under 100 x magnification (C) and 400 x magnification (D). E, F) Morphological image of Fusarium in Sabouraud's agar medium with grayish-white on the front (E) and yellow-brown on the back (F).

cases), metagenomic next-generation sequencing (2 cases), multilocus sequencing typing (1 case), and Sanger sequencing (1 case). Clinical presentations among the patients included multiple skin lesions and persistent fever. Additional symptoms included multiple nodules (4 cases), abscesses (4 cases), vision loss (3 cases), meningospondylodiscitis (2 cases), myalgia (1 case), and sinusitis (1 case). Classic treatment regimen involved combined therapy with AMB and VRC in 15 patients, while the remaining received AMB alone without VRC.

DISCUSSION

In 2021, the Global Guideline for the Diagnosis and Management of Rare Fungal Infections [21], jointly developed by the American Society for Microbiology (ASM), the International Society for Human and Animal Mycology (ISHAM), and the European Confederation of Medical Mycology (ECMM), highlighted *Fusarium* spp. as the most common clinical type among rare fungal infections. Most medically important *Fusarium* spp. fall into seven species complexes: *Fusarium solani* species complex (FSSC), *Fusarium oxysporum* species complex (FOSC), *Fusarium fujikuroi* species complex (FFSC), *Fusarium incarnatum-equiseti* species complex (FIESC), *Fusarium chlamidosporum* species complex (FCSC), *Fusarium dimerum* species complex (FDSC),

and *Fusarium sporotrichoides* species complex (FSAMSC) [1]. *Fusarium* bloodstream infections carry a high mortality in patients with hematologic diseases after HSCT. Immunocompromised patients are more likely to present with disseminated disease, while persistent neutropenia or neutrophil granulocyte deficiency (NGD) worsen the overall outcome and have been identified as the leading risk factor, as in the present case [22]. Neutropenic patients may continue to have positive blood cultures despite adequate antifungal therapy. Fungemia typically occurs from 1 to 10 days after the onset of skin lesions. In our case of a lymphoma patient undergoing NGD after HSCT, the patient developed fever and suspected mucocutaneous symptoms at + 1 day. Blood culture showed Fusarium infection at + 5 day. The painful nodules on the scrotum of this case were highly suspected to be a local infectious focus, but due to thrombocytopenia during transplantation, a tissue biopsy was not performed. Examination of tissue as soon as possible, especially skin biopsy from local lesions, can allow for rapid assessment before obtaining blood culture results.

Serum GM was moderately recommended as a diagnostic tool for detecting *Fusarium* infection in the 2021 guidelines [21]. It strongly advised monitoring serum GM levels in GM-positive patients during treatment. However, GM results may not accurately reflect *Fusarium* infection. In fact, the cross-reactivity of the external antigens of *Fusarium* with the GM test varies in reagents and species, as in the present case where all the patient's GM results in hospital were negative. Therefore, the definitive diagnosis of fusariosis still relies on positive culture of infected tissues or fluids as well as histopathological examination.

In 2022, the WHO classified *Fusarium* spp. as a high priority fungal pathogen due to significant antibiotic resistance. The 2021 guidelines [21] strongly recommend VRC or AMB as first-line treatments for invasive *Fusarium* disease. For critically ill patients, initial combination therapy is recommended. During the patient's fungemia, we conventionally used L-AMB combined with VRC for antifungal therapy, alongside the infusion of neutrophils from healthy donors, facilitating neutrophil recovery and reducing the duration of neutropenia (but the patient died). The antifungal susceptibility tests in our case showed low MIC of AMB (2.0 µg/mL), moderate MIC of VRC (4.0 µg/mL), and high MICs of itraconazole (> 16.0 µg/mL) and posaconazole (> 8.0 µg/mL), making achieving effective therapeutic levels challenging. But there is a lack of correlation between *in vitro* data and clinical outcomes [23]. The 2021 guidelines strongly recommend the susceptibility test for epidemiologic purposes, but weakly recommend the choice of antifungal therapy. It is important to note that AMB can cause nephrotoxicity, while VRC may lead to hepatotoxic reactions. Therefore, close monitoring of liver and kidney function is necessary during medication administration.

CONCLUSION

Fusarium bloodstream infection in patients with hematologic diseases after HSCT pose a high risk. This case highlights the fatal outcome and low cure rates associated with fusariosis, despite systemic combined antifungal treatment.

Ethics Approval:
Written informed consent was obtained from the patient's family members.

Declaration of Interest:
The authors declare that they have no known competing financial interests.

References:

1. Al-Hatmi AM, Hagen F, Menken SB, Meis JF, de Hoog GS. Global molecular epidemiology and genetic diversity of Fusarium, a significant emerging group of human opportunists from 1958 to 2015. Emerg Microbes Infect 2016;5(12):e124. (PMID: 27924809)

2. Cho CT, Vats TS, Lowman JT, Brandsberg JW, Tosh FE. Fusarium solani infection during treatment for acute leukemia. J Pediatr 1973;83(6):1028-31. (PMID: 4518930)

3. Cortelazzo S, Ferreri A, Hoelzer D, Ponzoni M. Lymphoblastic lymphoma. Crit Rev Oncol Hematol 2017;113:304-17. (PMID: 28427520)

4. Yun SJ, Shin MG, Choi C, et al. Fatal disseminated angioinvasive Fusarium falciforme infection in a patient with acute myeloid leukaemia. Br J Dermatol 2007;157(2):407-9. (PMID: 17573871)

5. Kah TA, Yong KC, Rahman RA. Disseminated fusariosis and endogenous fungal endophthalmitis in acute lymphoblastic leukemia following platelet transfusion possibly due to transfusion-related immunomodulation. BMC Ophthalmol 2011;11:30. (PMID: 22044440)

6. Liu JY, Chen WT, Ko BS, et al. Combination antifungal therapy for disseminated fusariosis in immunocompromised patients : a case report and literature review. Med Mycol 2011;49(8):872-8. (PMID: 21449694)

7. Fan F, Lui G, Ip M, Lee N. Foot ulcer, skin nodules, and blurred vision. Clin Infect Dis 2012;54(5):706, 736-7. (PMID: 22322270)

8. Cheng P, Meng F, Zhang D. Fatal Fusarium solani infection after stem cell transplant for aplastic anemia. Exp Clin Transplant 2014;12(4):384-7. (PMID: 24679137)

9. Das K, Bhattacharyya A, Chandy M, et al. Infection control challenges of infrequent and rare fungal pathogens: lessons from disseminated Fusarium and Kodamaea ohmeri infections. Infect Control Hosp Epidemiol 2015;36(7):866-8. (PMID: 25998614)

10. Chiewchanvit S, Chongkae S, Mahanupab P, et al. Melanization of Fusarium keratoplasticum (F. solani Species Complex) During Disseminated Fusariosis in a Patient with Acute Leukemia. Mycopathologia 2017;182(9-10):879-85. (PMID: 28616680)

11. Kurosawa S, Sekiya N, Muraosa Y, et al. [Disseminated fusariosis in patients with acute leukemia: a retrospective analysis of three cases]. Rinsho Ketsueki 2017;58(12):2375-9. (PMID: 29332869)

12. Okada K, Endo T, Hashimoto D, et al. Disseminated fusariosis emerged from prolonged local genital infection after cord blood transplantation. J Infect Chemother 2018;24(8):660-3. (PMID: 29373264)

13. Yu J, Chen Y, Fang J, Zhang K. Successful treatment of disseminated fusariosis in a patient with acute lymphoblastic leukemia: A case report and literature review. Medicine (Baltimore) 2019; 98(26):e16246. (PMID: 31261588)

14. Ang A, Chew KL. Disseminated Fusarium solani complex infection. Clin Microbiol Infect 2020;26(12):1636-7. (PMID: 32540471)

15. Fujishita K, Oka S, Kamei K, et al. A Disseminated Fusarium fujikuroi Species Complex Infection Prior to Allogeneic Hematopoietic Stem Cell Transplantation. Acta Med Okayama 2020;74 (5):435-41. (PMID: 33106701)

16. Ning JJ, Li XM, Li SQ. Disseminated Fusarium bloodstream infection in a child with acute myeloid leukemia: A case report. World J Clin Cases 2021;9(21):6049-55. (PMID: 34368326)

17. Lin ZL, Zhang XL, Guo PH, et al. [Acute myeloid leukemia accompanied with invasive fusariosis in a child]. Zhonghua Er Ke Za Zhi 2022;60(8):831-3. (PMID: 35922199)

18. Fei H, Liu X, Sun L, et al. Disseminated fusarium infection after allogeneic hematopoietic stem cell transplantation after CART: A case report. Medicine (Baltimore) 2022;101(45):e31594. (PMID: 36397380)

19. Zhong L, Song Y, Hu J, Yao X, Li T, Li H. Successful treatment of disseminated amphotericin-resistant fusariosis in a paediatric patient with acute lymphoblastic leukaemia: a case report and literature review. Eur J Dermatol 2022;32(5):623-8. (PMID: 36468720)

20. Kim JY, Kang CI, Lee JH, et al. Clinical Features and Outcomes of Invasive Fusariosis: A Case Series in a Single Center with Literature Review. Infect Chemother 2023;55(2):290-4. (PMID: 34227751)

21. Chen SC, Perfect J, Colombo AL, et al. Global guideline for the diagnosis and management of rare yeast infections: an initiative of the ECMM in cooperation with ISHAM and ASM. Lancet Infect Dis 2021;21(12):e375-e386. (PMID: 34419208)

22. Samborska M, Wziatek A, Mlynarczyk L, Dey S, Varghese N, Derwich K. Fusarium oxysporum disseminated infection in a teenage patient with a relapse of acute lymphoblastic leukemia - Case report and review of the literature. J Infect Chemother 2024;30(3):258-62. (PMID: 37913869)

23. Nucci M, Jenks J, Thompson GR, et al. Do high MICs predict the outcome in invasive fusariosis? J Antimicrob Chemother 2021;76 (4):1063-9. (PMID: 33326585)

24. Nucci M, Anaissie E. Invasive fusariosis. Clin Microbiol Rev 2023;36(4):e0015922. (PMID: 37937988)