Clinical Case Report

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Successful treatment of disseminated fusariosis in a patient with acute lymphoblastic leukemia

A case report and literature review

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Abstract

Rationale: *Fusarium* is the second most common cause of fungi infections in the immunocompromised patients with the mortality rate over 80%. Early identification and appropriate selection of antifungal drugs is the key to successful treatment.

Patient concerns: A 31-year-old female was diagnosed with acute lymphocytic leukemia (pro-B ALL). She developed a high fever and presented with typical painful purple nodules with central necrosis formed on the upper and lower limbs during the induction chemotherapy.

Diagnosis: Combining clinical manifestations with results of blood culture testing and sequencing methods, it was consistent with the diagnosis of disseminated fusariosis.

Interventions: The patient was treated with the combination of tigecycline and antifungal agents (Liposomal Amphotericin B and Voriconazole),

Outcomes: The skin lesions generally healed with some scar left after treating with antifungal agents for 6 weeks. The final date of follow-up was 1.5 years later, and the patient was alive with no diseases.

Lessons: This case highlights the importance of the typical cutaneous lesions for early diagnosis and proper treatment to decrease the mortality rate of this severe infection. This patient was successfully treated with the combination of tigecycline and antifungal agents, which may be the first clinical confirmation of tigecycline that improved the effectiveness of antifungal agents against fusariosis, but it requires more studies to verify. We reviewed 62 cases from literature and analyzed using logistic regression and recognized the high-risk factor for fusariosis mortality in patients with acute leukemia was non-remission of underlying disease.

Abbreviations: ALL = acute lymphoblastic leukemia, AMB = amphotericin B, ANC = absolute neutrophil count, MIC = minimum inhibitory concentration, PB = peripheral blood, PICC = peripherally inserted central catheter, TGC = tigecycline, VRC = voriconazole.

Keywords: acute lymphoblastic leukemia, amphotericin B, fusariosis, tigecycline, voriconazole

1. Introduction

Fusarium is an opportunistic fungal pathogen,[1] which is the second most common cause of fungi infections in the immunocompromised patients.[2] Infection of *Fusarium* often localizes on the skin, presenting as purple nodules with central necrosis. Such infection can become invasive and disseminated especially in individuals with neutropenia after chemotherapy or hematopoietic stem cell transplantation (HSCT).[3,4] The lack of identification of *Fusarium* infection accounts for the low early diagnosis rate and the resistance to various antifungal drugs,[5] both of which lead to a poor prognosis with the mortality rate over 80%.[6] Therefore, understanding the clinical characteristics of *Fusarium* infection, early identification and appropriate selection of antifungal drugs, including amphotericin B (AMB) and voriconazole (VRC),[7–9] are the keys to successful treatment.

2. Case report

A 31-year-old female was admitted to the hospital with dizziness and ecchymosis for half a month in May 2017. The patient was finally diagnosed with acute lymphocytic leukemia (pro-B ALL). She received pretreatment with an intravenous drip of dexamethasone (10 mg/day). After 7-day treatment, her lymphocyte count decreased to $<1.0 \times 10^9$/L. Then she received induction chemotherapy with VICP (vincristine 2 mg, on days 1, 8, 15, and 22; idarubicin 10 mg, on days 1–3; cyclophosphamide 1.0 g, on day 1; and prednisone 50 mg, on days 1–14, 30 mg, on days 15–28). At the same time, VRC was taken orally to prevent fungal infections.

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The written consent has obtained from the patient for publication of this case report and accompanying images.

The authors have no conflicts of interest to disclose.

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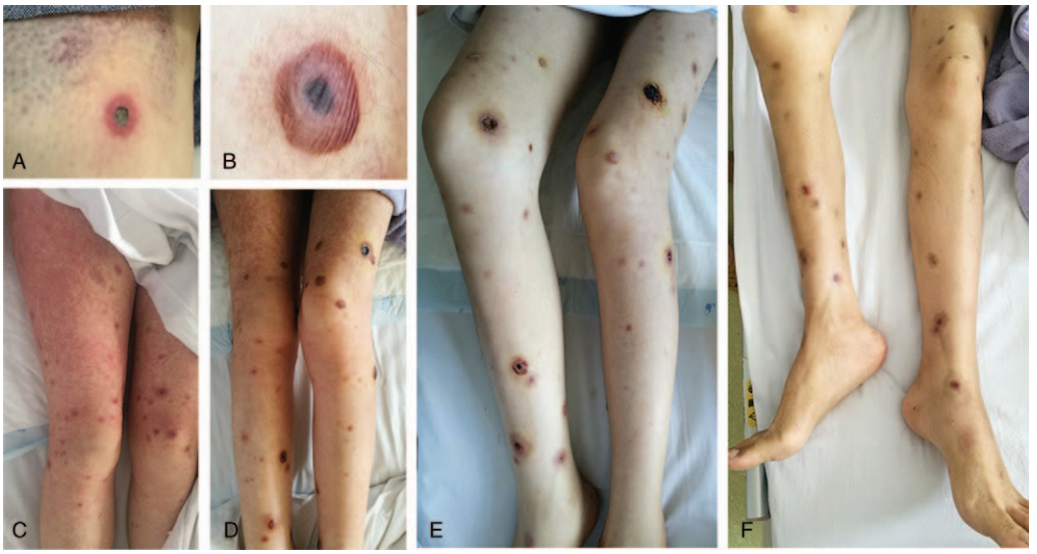

Figure 1. Cutaneous lesions. (A) On day 11, both lower limbs began to appear the purple papules accompanied by mild itching. A pitted black necrotic black scab showed in the center. (B) On day 15, the papule was prominent on the surface of the body, and the central necrotic black callus presented a redness and swelling, accompanied by pain and abscess exudation. (C) On day 17, the papules spread throughout the whole body. (D) On day 32, the papules gradually recovered, partial scab fell off and developed into deep ulcers. (E) On day 64, the papules healed, multiple brown hard knots remained in the skin. (F) After half a year of *Fusarium* spp. infection, the skin lesions generally healed and the scar left.

Four days after the beginning of induction chemotherapy, the patient developed a low fever (37.5°C–38.2°C) and neutropenia (absolute neutrophil count [ANC] 0.18×10^9/L). The blood culture testing was performed and the result was negative. Chest computed tomography scan simply demonstrated a few small nodules in the field of both lungs. She was treated with cefotaxime and moxifloxacin. On day 7, she developed a high fever with chills, reddish rashes appeared on both legs with no pain or itching, and neutropenia continued (ANC: 0.02×10^9/L). The blood culture testing was performed again while with a negative result. We replaced the antibiotics with imipenem and teicoplanin. Granulocyte colony-stimulating factor (G-CSF; 300 μg once daily) was given to facilitate the release of neutrophils from the bone marrow and improve neutrophil function. However, she still had a high fever. On day 11, the center of papules began to show black necrosis with mild itching, then the papules developed into pustules (Fig. 1A). We performed abscess and blood culture (Peripherally Inserted Central Catheter [PICC] together with Peripheral Blood [PB]) testing and replaced teicoplanin with linezolid. On day 15, the papules ruptured, and the rashes developed into black eschar with pain (Fig. 1B). On day 17, she still had a high fever, and new quats appeared all over the body (Fig. 1C), so we stopped linezolid and treated her with tigecycline (TGC). On day 18 (just 1 day after the first TGC treatment), the patient had a normal body temperature, then recovered from neutropenia (ANC: 4.05×10^9/L). On day 20, the blood culture (both PICC and PB) testing performed on day 11 showed *Fusarium* growing (Fig. 2). We removed the PICC and started antifungal therapy with liposomal

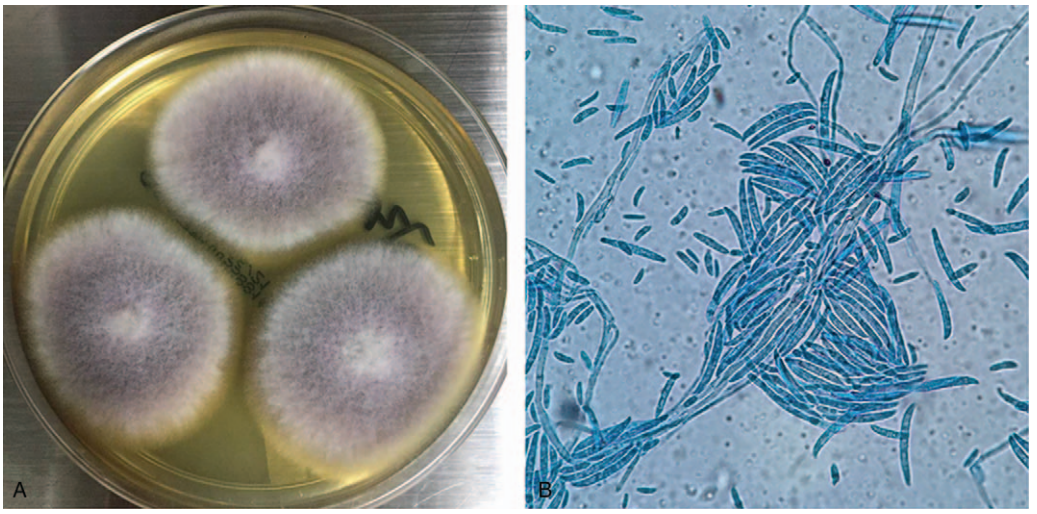

Figure 2. The *Fusarium solani*. from blood culture. (A) The morphologic image of *Fusarium solani.* in Sabouraud's agar medium. (B) The microscopic image of *Fusarium solani.* stained with lactophenol cotton blue under 1000 × magnification.

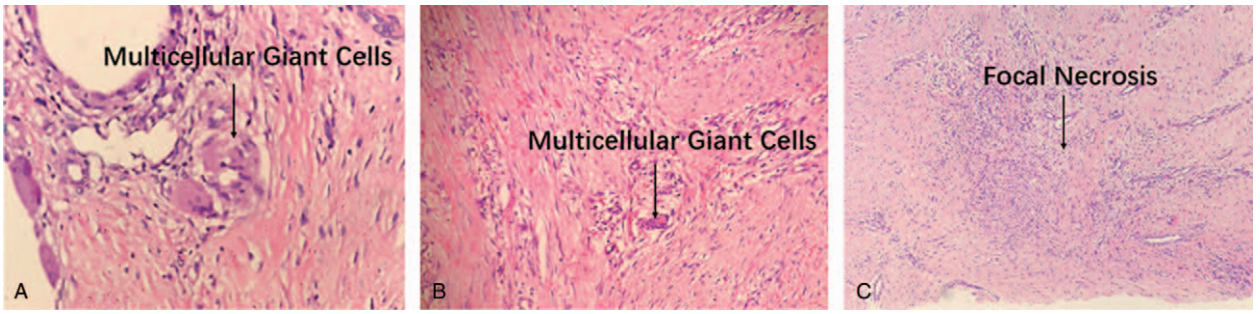

Figure 3. Skin Biopsy (scar on the left lower limb). Hematoxylin and Eosin (H&E) stained skin section under (A) 400× magnification; (B,C) 100× magnification. We can see necrosis in deep dermal foci with the inflammatory cells, histocyte and plenty of multicellular giant cells, which consistent with granulomatous changes. Pathologically, the skin lesions were consistent with fungal infection but no *Fusarium* found.

amphotericin B (L-AMB) immediately. After 2 weeks' therapy with L-AMB, VRC, and TGC, the papules gradually recovered, partial scab fell off and developed into deep ulcers (Fig. 1D). Bone marrow aspiration revealed <5% lymphoblasts, indicating she had achieved a complete hematologic remission with incomplete blood count recovery. She had received L-AMB combined with VRC treatment for 6 weeks. She stopped antifungal therapy after twice negative blood cultures testing and negative biopsy examination of the cutaneous lesions (Fig. 3). On day 64, the papules healed and left with multiple brown hard knots (Fig. 1E). After half a year of *Fusarium* infection, the skin lesions generally healed with some scar left (Fig. 1F). The final date of follow-up was December 26, 2018, and the woman was alive with no diseases.

2.1. Fungal identification and antifungal susceptibility test

We sequenced the DNA of strain on blood culture. The fungus strains' ribosomal RNA (rRNA) gene internal transcribed spacer (ITS) sequences tested by PCR amplification and sequencing methods were analyzed and compared with similar sequences from GENBANK by NCBI BLAST online tool and DNAMAN software (https://blast.ncbi.nlm.nih.gov/Blast.cgi). The results turned to *Fusarium solani*, the most common fungus.

Because of the addition of TGC to antifungal agents of VRC, the patient recovered from high fever. To explore the synergistic combination of TGC with antifungal agents, VRC or AMB, against *Fusarium*, a simple drug sensitivity test was conducted according to the broth microdilution method (M38-A2). The results show in Table 1. There are few reference standards for susceptibility of *Fusarium*, and we did not find its minimum inhibitory concentration (MIC) reference standard on Clinical & Laboratory Standards Institute (CLSI) guidelines. Therefore, this experiment referred to *Fusarium moniliforme Sheld* (ATCC MYA-3629) in the health industry standard of the People's Republic of China (WS/T 411–2013). The reference MIC range of 5-Flucytosine and Fluconazole were absent but their MIC was both at the maximum, which indicating resistance. The results showed that this *F solani* was more sensitive to AMB than VRC. Unfortunately, our test did not show the synergistic combination of TGC with antifungal agents against *F solani*.

2.2. Literature review

We comprehensively collected data from Web of Knowledge, PubMed, Elsevier, SpringerLink, WILEY and other databases with the keywords of "*Fusarium* Infection AND case report", "Leukemia" and 76 cases were collected.[10–31] Reports included cases in the final analysis with data on age, sex, neutrophil count, the site of infection, underlying disease, bone marrow transplantation, corticosteroid exposure, antifungal prophylaxis, treatment, and the stage of the underlying disease. Data analysis performed by SPSS 24.0 statistical software. Our bivariate analyses consisted of the chi-square test and Fisher exact test if necessary. Univariate non-conditional logistic regression analysis performed with unfavorable outcomes as dependent variables. $P < .05$ was considered as statistically significant.

A total of 62 cases of acute leukemia were selected and summarised in Table 2. The median survival was 39 days in the death group. For the multivariable analyses, we performed unconditional logistic regression, first we examined sex, age, the outcome of blood culture, underlying disease, bone marrow transplantation, corticosteroid exposure, antifungal prophylaxis, treatment, and the stage of underlying disease as the sole explanatory variable of the logistic regression model. Then we assessed the adjusted underlying disease status in a final main-effects model that was constructed through backward selection to select statistically significant variables at $P = .05$ (Table 3). The mortality rate of patients with non-remission of primary disease was 6.667 times.

Table 1

In vitro susceptibility of *Fusarium* to antifungal and antimicrobial agents.

Antifungals	MIC, μg/mL	MIC μg/mL (WS/T 411-2013),	Sensitivity assessment
5-FU	16	–	R
AMB	0.5	2.0–8.0	S
FCA	256	–	R
ITR	8	>8	R
VRC	1	1.0–4.0	S
5-FU+TGC	16	–	R
AMB+TGC	0.5	2.0–8.0	S
FCA+TGC	256	–	R
ITR+TGC	8	>8	R
VRC+TGC	1	1.0–4.0	S

5-FU = 5-flucytosine, AMB = amphotericin B, FCA = fluconazole, ITR = itraconazole, MIC = minimum inhibitory concentration, R = resistant, S = susceptible, TGC = tigecycline, VRC = voriconazole; health industry standards of the People's Republic of China on antifungal susceptibility testing of filamentous fungi-broth dilution method, WS/T 411-2013.

Table 2

General information of 62 cases of acute leukemia with *Fusarium* infection.

Factor		Death Group(n = 30)	Cure Group(n = 32)	*P*
Median age, Yr		42	53	.97
The Median Time to start antifungal therapy, Day		16.5	15	.14
Neutrophil deficiency, n/%		27/46.6	31/53.4	.30
After Diagnosis 30–50 day Median Neutrophil count ($\times 10^9$/L)		0.197	0.6	.21
Sex, n/%	Male	20/50.0	20/50.0	.73
	Female	10/45.5	12/54.5	
Positive Blood Culture, n/%		19/54.3	16/45.7	.58
Underlying Disease n/%	ALL	9/42.9	12/57.1	.53
	AML	21/51.2	20/48.8	
Bone marrow transplantation, n/%		6/66.7	3/33.3	.23
Use Glucocorticoids, n/%		8/38.10	13/61.90	.24
Antifungal prophylaxis, n/%	5/45.5	6/54.5	0.83	
Treatment, n/%	AMB or VRC	10/58.8	7/41.2	.50
	AMB or VRC plus other Antifungal Drug	18/45.0	22/55.0	
	Do not use AMB or VRC	2/40.0	3/60.0	
Complete remission of underlying disease, n/%		16/41.0	23/59.0	.03

All significance testing was done at the $P < .05$ level; ALL = acute lymphoblastic leukemiA, AMB = amphotericin B, AML = acute myelogenous leukemia, VRC = voriconazole.

3. Discussion

Fusarium is an opportunistic human pathogen severely affecting immunocompromised patients, especially the patients with hematological malignancies, prolonged neutropenia and after receiving hematopoietic stem cell transplantation.[2–4] This patient of pro-B ALL was immunocompromised with profound neutropenia, history of corticosteroid exposure and broad-spectrum antibiotics, which may increase chances of opportunistic infections despite antifungal prophylaxis with VRC.

Localized infections, such as endophthalmitis and skin infections can influence on the immunocompetent individuals associated with trauma.[32–35] The invasive and disseminated infections predominantly in severely immunocompromised individuals since the *Fusarium* can invade blood vessels.[2,36,37] According to our results of literature review and statistic analysis, the high-risk factor for fusariosis mortality in patients with acute leukemia was non-remission of underlying disease ($P < .05$). The mortality rate in patients with primary disease non-remission is 6.667 times than these remission patients. Though other risk factors for *Fusarium* infection mortality are not significant in our study, the duration of neutropenia, the time to start antifungal therapy, positive blood culture, and bone marrow transplantation may have certain relation with the death rates of *Fusarium* infection,[38–41] which may due to the small group of cases with distinct clinical menifestation reported by different institutes.

Fusarium infection has an inferior prognosis. The key to successful treatment is to reverse immunosuppression and to receive correct antifungal therapy as soon as possible.[42] Therefore, it is particularly important to identify *Fusarium* infection. *Fusarium* can disseminate in severely immunocompromised individuals. Most cases can present with cutaneous lesions.[43] In 35 cases with positive blood culture of our literature review, 23 cases had skin manifestations. It is worth noting that the skin lesions can be the only early manifestation. The typical painful purple lesions with pitted black necrotic in the center on the arms and legs can help early identify the *Fusarium* infection. This case highlights the importance of cutaneous lesions for the early diagnosis of *Fusarium* infection.

Table 3

Multivariate Logistic Regression Analysis of the death in patients with acute leukemia complicated with *Fusarium* spp. infection.

Factor	β	SE	Wald	*P*	OR	95% CI
PR or NR	1.897	0.899	4.452	.04	6.667	1.145–38.833

All significance testing was done at the $P < .05$ level; NR = non-remission, OR = odds ratio, PR = partial remission.

Appropriate selection of antifungal drugs is essential to decrease the mortality rate of this severe infection. *Fusarium* show broad in vitro resistance to antifungal agents. AMB considered being the most effective drug against *Fusarium*,[44] followed by VRC.[45] Posaconazole can be used for refractory cases.[5] Nonetheless, the usage of monotherapy for the treatment of systemic fusariosis is unsatisfactory owing to high rates of resistance against antifungal agents. In this regard, combined therapies have been designed in an attempt to overcome antifungal resistance. There are studies showing that AMB and VRC have synergism.[46–47] In recent years, numbers of researchers focus on the combination of antibiotics and antifungal drugs to treat fungal infection. A study conducted by Rossato et al[48] on the interaction of antifungal and antibacterial drugs in vitro indicated that synergistic interactions between AMB and azithromycin (AZM), daptomycin (DAP), linezolid (LZD), or TGC against clinical isolates of *Cryptococcus neoformans var. grubii*. The synergy may be explained by the ability of AMB to form pores through the plasma membrane of the yeast cells, facilitating the entrance of the antibacterial agents, thus leading to inhibition of protein synthesis. Jesus FPK[49] reported the synergistic combinations of AMB and TGC against *Pythium insidiosum* in *vitro*. The synergistic combinations of AMB, VRC, and TGC against *Fusarium* was also confirmed in vitro.[50] In this case, we added TGC on the basis of intravenous VRC and reduce the fever. This patient may be the first successful case treated combining TGC with antifungal agents against *Fusarium* and did have the synergism.

We further investigate *in vitro* synergistic combinations of TGC with antifungal agents against *F solani*. Our results did not show the synergistic combinations of TGC with antifungal

agents. The possible reasons are as follows: poor laboratory conditions, differences of in vivo and in vitro, inaccuracy of TGC concentration preparation, too much inoculation of strains and insufficient concentration of antibiotics. Though our result was different from the literature report, this patient was successfully treated with the combination of TGC and antifungal agents against *Fusarium*. TGC may help improve the effectiveness of antifungal agents against fusariosis, which requires further clinical trials to verify. Besides, the removal of venous catheters, reversal of immunosuppression and early recovery from neutropenia may contribute to the patient successful treatment against *Fusarium*.

Author contributions

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Formal analysis: Jieni Yu.
Funding acquisition: Kejie Zhang.
Methodology: Kejie Zhang.
Project administration: Yan Chen.
Resources: Kejie Zhang, Yan Chen, Jiabin Fang.
Supervision: Jiabin Fang.
Visualization: Jiabin Fang.
Writing – original draft: Jieni Yu.
Writing – review & editing: Kejie Zhang.

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