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Contents

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## REVIEW



## MINIREVIEWS



## ORIGINAL ARTICLE

### Case Control Study



### Retrospective Cohort Study



### Retrospective Study

*World Journal of Clinical Cases*

**Thrice Monthly Volume 9 Number 21 July 26, 2021**

## Contents

*World Journal of Clinical Cases*

**Thrice Monthly Volume 9 Number 21 July 26, 2021**

## Contents

*World Journal of Clinical Cases*

**Thrice Monthly Volume 9 Number 21 July 26, 2021**

## Contents

## ABOUT COVER

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## AIMS AND SCOPE

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CASE REPORT

# Disseminated *Fusarium* bloodstream infection in a child with acute myeloid leukemia: A case report

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**Author contributions:** Ning JJ was the patient's doctor, reviewed the literature, and contributed to drafting the manuscript; Li XM provided the plans for the treatment; Li SQ was the nurse in charge of the child and provided skin pictures of various periods; all authors issued final approval of the version to be submitted.

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## Abstract

### *BACKGROUND*

Disseminated *Fusarium* is rare in healthy children. Children with hematological tumors may have secondary fungal infections, including *Fusarium* infections, which are due to tumor bone marrow infiltration or prolonged bone marrow suppression after chemotherapy. Because of the lack of typical clinical manifestations and effective antifungal drugs, early diagnosis and treatment of the disease are difficult, and the prognosis is poor.

### *CASE SUMMARY*

The patient in this case was a 13-year-old female child with rash and fever as the first symptoms. She had the characteristics of the four stages of skin that are typical of *Fusarium* infection. She was diagnosed with disseminated *Fusarium* infection through skin biopsy and blood culture and diagnosed with *Fusarium solani* infection based on the morphological characteristics of the blood culture. After treatment with liposome amphotericin B combined with voriconazole, the child recovered.

### *CONCLUSION*

This case highlights that for children with secondary agranulocytosis after receiving chemotherapy for hematological malignancies, once typical abnormal skin damage is found, the possibility of *Fusarium* infection should be considered, and voriconazole alone or in combination with polyenes may be the most effective anti-*Fusarium* drugs. Amphotericin B, the traditional drug of disseminated *Fusarium* disease, has a high mortality rate, and it is not recommended to use it alone. Adequate neutrophil counts are essential for the treatment of disseminated *Fusarium* bloodstream infection.

**Key Words:** *Fusarium*; Liposomal amphotericin B; Voriconazole; Acute myeloid leukemia; Agranulocytosis; Case report

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**Core Tip:** We present herein the case of a *Fusarium* infection female child with rash and fever as the first symptoms. She had the characteristics of the four stages of skin typical of *Fusarium* infection. She was diagnosed with disseminated *Fusarium* infection through blood culture. For children with secondary agranulocytosis after receiving chemotherapy for hematological malignancies, once typical abnormal skin damage is found, the possibility of *Fusarium* infection should be considered, and the key to treatment is early diagnosis, the reversal of immunosuppression, and the provision of the correct antifungal treatment as soon as possible.

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## INTRODUCTION

*Fusarium* was discovered in 1958 and is a common soil mold. It was once considered to be pathogenic only in plants and to be able to cause devastating diseases in plants and crops[1]. However, Cho *et al*[2] first reported a case of disseminated *Fusarium* bloodstream infection in a child with acute myeloid leukemia in 1973 and found that *Fusarium* could also infect humans. With the increasing number of patients with low immune function, *Fusarium* is considered to be the second most common filamentous fungus that causes opportunistic infections after *Aspergillus*, and *Fusarium* infections are reported every year[3]. In this study, the clinical manifestations, diagnosis, and treatment of a case of disseminated *Fusarium* bloodstream infection in a child with acute myeloid leukemia are reported to provide a reference for future clinical treatment.

## CASE PRESENTATION

### *Chief complaints*

The patient, a 13-year-old Chinese girl, came to our hospital because she had a pale complexion for 1 mo.

### *History of present illness*

One month prior to presentation, the child appeared pale, which gradually worsened. Laboratory examination indicated the following: White blood cell count (WBC) 1.54 × $10^9$/L, N% 7.9%, hemoglobin (Hb) 47 g/L, and platelets (PLT) 64 × $10^9$/L. The results of bone marrow cell morphology, immunology, and cellular and molecular genetics (MICM typing) confirmed acute myeloid leukemia (type M1). Then, the patient received induction DA chemotherapy (daunorubicin for 3 d and cytarabine for 7 d).

### *History of past illness*

The patient had an unremarkable previous medical history.

### *Personal and family history*

The patient's personal and family history was nothing special.

### *Physical examination*

On the third day after induction chemotherapy, the child developed a high fever. Physical examination revealed maculopapules on the face, trunk, and extremities (Figure 1A). The rash was further aggravated, mainly on the trunk, with obvious tenderness, part of the rash showed central necrosis and obvious peripheral swelling (Figure 1B), and part of the rash manifested vesicular formations (Figure 1C). Subsequently, the rash further changed, and the vesicular lesions ruptured to form

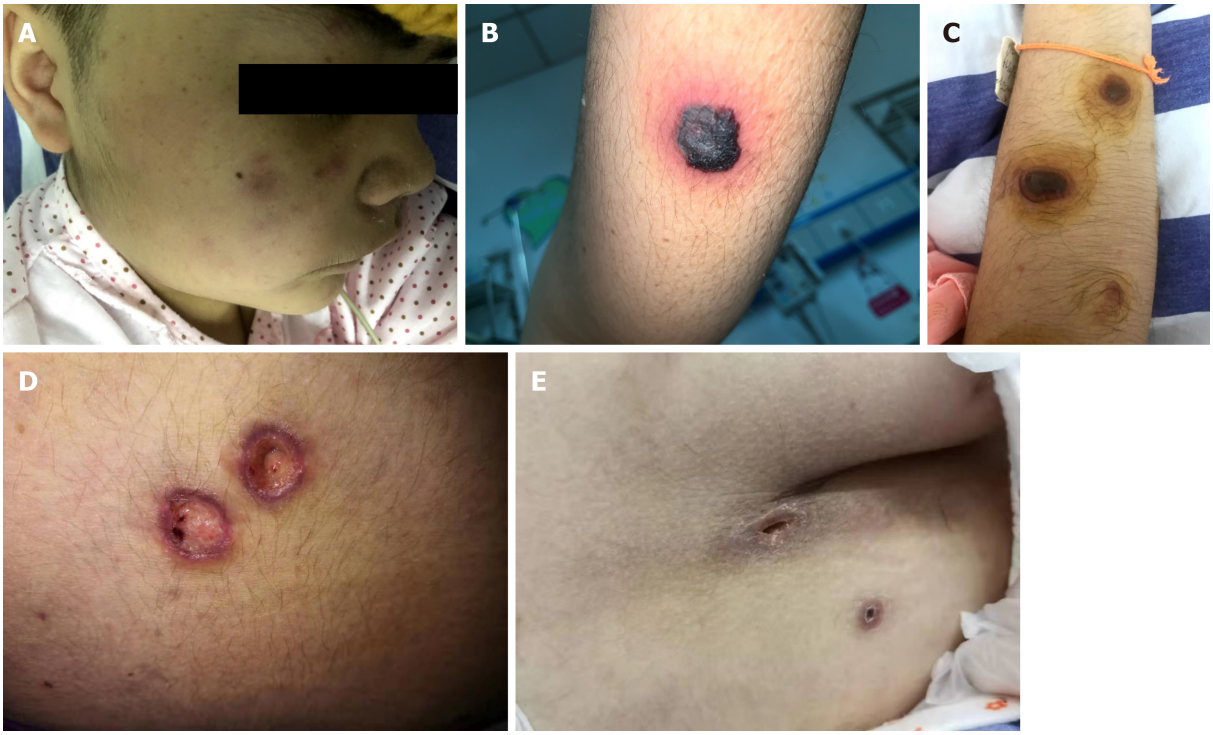


**Figure 1 Skin lesions.** A: The cheeks, limbs, and trunk began to show purple macules with mild itching; B: Papules protruded from the body surface, with black necrotic tissue visible in the center, peripheral redness and swelling, and accompanying pain; C: Herpes-like lesions with pus were seen in the center of the rash; D: Once the scabs fell off, the affected areas developed into deep ulcers; E: The ulcers gradually healed, leaving scars.

crater-like ulcers (Figure 1D).

### *Laboratory examinations*

Myelosuppression occurred during chemotherapy, repeated full blood examination demonstrated persistent neutropenia (WBC 0.12 × $10^9$/L and absolute neutrophil count 0.01 × $10^9$/L), and C-reactive protein was 296.5 mg/L. Two repeated fungal antigen tests [galactomannan (GM) and β-D-glucan] were negative.

### *Imaging examinations*

Computed tomography (CT) examination of the chest and abdomen showed no involvement of deep organs.

### *Microbiological identification of the causative agent*

The blood culture grew a fungus, which was ultimately identified as *Fusarium solani* by morphological characteristics (Figure 2). Fungi were seen on the biopsy of the exfoliated scab (Figure 3).

## FINAL DIAGNOSIS

The final diagnosis of the presented case was disseminated *Fusarium* bloodstream infection.

## TREATMENT

This child had febrile neutropenia, combined with skin rash as the main clinical manifestation. On the basis of imipenem and cilastatin sodium anti-infection, vancomycin was added to cover Gram-positive microorganisms. Fluconazole was used to prevent fungal infection, and granulocyte colony-stimulating factor was used to promote the recovery of hematopoietic function. However, the rash was further aggravated, and the child still suffered from repeated high fever and altered conscious state and feeding. The antibacterial drugs imipenem and cilastatin sodium and

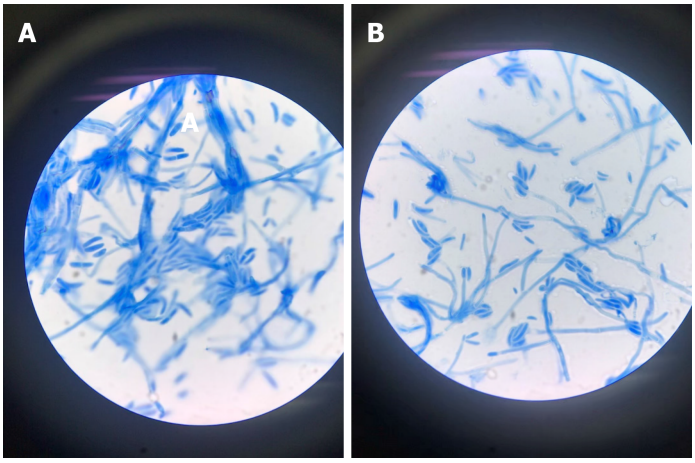


**Figure 2 Microscopic images (1000 ×) of *Fusarium solani* stained with lactophenol cotton blue.** A: The macroconidia are stout and sickle-shaped; B: Septated hyphae with straight simple thin long phialide bearing oval microconidia in a "diphtheroidal" pattern.

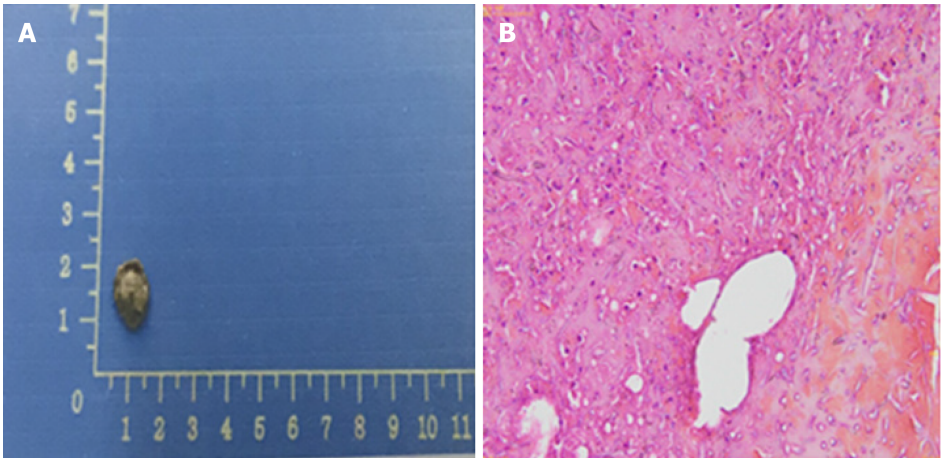


**Figure 3 Fungi were seen on the biopsy of the exfoliated scab.** A: Exfoliated scab examination; B: Fungi can be seen in the scab.

vancomycin continued to be given to treat infection. Considering the high drug-resistance rate of *Fusarium* and the poor prognosis of patients with low immunity and disseminated *Fusarium* infection, fluconazole was changed to voriconazole and liposomal amphotericin B to ensure that at least one drug was effective (Figure 4). After the body temperature stabilized, the antibiotic regimen was downgraded to cefoperazone sodium and sulbactam sodium for continued prevention of infection, and the administration of liposomal amphotericin B combined with voriconazole antifungal treatment was continued for 4 wk.

## OUTCOME AND FOLLOW-UP

The child had a fever for 14 d. After that, the body temperature was normal, and the necrotic rash gradually healed (Figure 1E). Routine blood re-examination showed the following: WBC 8.76 × 109/L, neutrophil 7.26 × $10^9$/L, Hb 70 g/L, PLT 35 × $10^9$/L, and CRP 88.7 mg/L. However, before discharge, a 4 cm × 1.5 cm mass was palpable in the right calf of the child, and the tenderness was obvious. B-scan ultrasonography showed the formation of a local abscess, and CT examination of the chest and abdomen showed no involvement of deep organs. The discharge instructions were to continue posaconazole oral suspension combined with cefixime for anti-infection treatment for 2 wk. Eventually, the clinical symptoms of the child disappeared, the blood culture was negative on re-examination, and a clinical cure was achieved. There were no obvious adverse drug reactions during the treatment. However, the second cycle of chemotherapy was delayed because of the fungal infection. At present, the child is generally in good condition, and a second round of chemotherapy is planned.

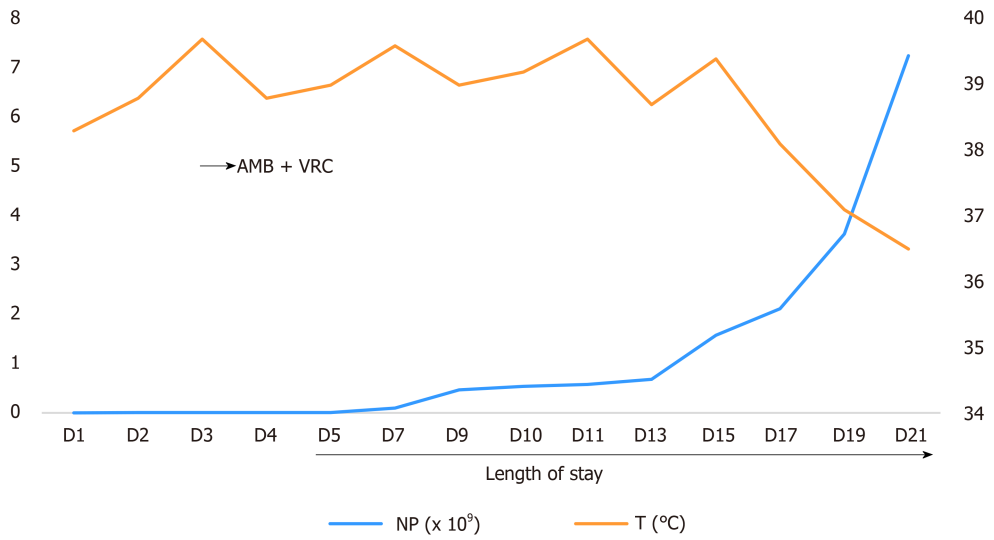


**Figure 4 Changes in body temperature and neutrophils before and after medication (D5: The growth of *Fusarium* in blood culture).** AMB: Amphotericin B; VRC: Voriconazole; NP: Neutrophil.

## DISCUSSION

*Fusarium* is a saprophytic fungus with strong ecological adaptability. It is widely distributed in natural soils and plants and can even live in deserts and Arctic regions. It can be parasitic on animal and plant bodies or saprophytic in animal and plant debris. Some species can produce mycotoxins under certain circumstances and threaten the health of humans and animals[4]. A multicenter retrospective study indicated a significantly increased incidence of *Fusarium* infection in patients with immunosuppression and acute myeloid leukemia, and this type of infection ranks second only to *Aspergillus* infection[5]. For people with normal immunity, *Fusarium* is an opportunistic pathogen, mainly causing local infections[6], but for patients with hematological malignancies, aplastic anemia, and organ transplantation or undergoing chemotherapy, *Fusarium* can cause invasive fungal infections. Among these patients with low immune function, disseminated *Fusarium* disease accounts for 70% of *Fusarium* infections[7].

In immunocompromised hosts, the lack of a normal immune response can lead to vascular infiltration of *Fusarium*, leading to necrosis and diffuse infection, with skin involvement in 70% of cases of *Fusarium* infection[8]. The characteristic skin lesions may provide guidance for the early diagnosis of *Fusarium* infection. A typical *Fusarium* infection-induced rash can be divided into four periods: Stage I, red maculopapular rash; stage II, necrosis in the center of the rash; stage III, vesicular bullae changes secondary to necrosis; and stage IV, after the eruption, the vesicular lesions change to cratered lesions and eventually heal. Each period of skin change is 1-2 d apart[9]. The rash in this case showed typical four-stage manifestations. This study found that the four stages of *Fusarium* skin lesions can coexist, and in stage III, the vesicular lesions presented as thick-walled blisters with cloudy pus, and pain was obvious during the rash. Although the rash caused by *Fusarium* infection is specific, it still needs to be distinguished from the rash of patients with neutropenia, including leukemic deposits, viral infections, bacterial infections (ecthyma gangrenosum), and other fungi ( *Aspergillus*, mucormycosis, and *Candida*) causing skin lesions.

*Fusarium* infection is difficult to cure and has a poor prognosis; the overall mortality is as high as 50%-70%[10], and there is no consensus on the management of invasive disseminated *Fusarium* infection in the case of neutropenia. At present, the key to successful treatment is early diagnosis, the reversal of immunosuppression, and the administration of the correct antifungal treatment as soon as possible; however, *Fusarium* has shown widespread resistance to antifungal drugs *in vitro*. *In vitro* studies suggest that fluconazole, itraconazole, and flucytosine are not effective against *Fusarium*, while ketoconazole, miconazole, terbinafine, and voriconazole have limited efficacy. Amphotericin B is considered to be the most effective anti-*Fusarium* drug *in vitro*. However, Nucci *et al*[7] showed that the mortality rate of amphotericin B in the treatment of disseminated *Fusarium* was as high as 70%. The current successful

treatment often comes from cases of voriconazole, so voriconazole alone or in combination with polyenes has been increasingly used for *Fusarium* infections. Because of the high drug resistance rate of *Fusarium*, the use of a single drug for the treatment of drug-resistant fungi cannot achieve a satisfactory effect, but a major concern for combination therapy is the potential antagonistic effect between antifungal agents. Some studies have shown that liposomal amphotericin B combined with voriconazole has a synergistic effect in the treatment of drug-resistant fungi[11]. Ho *et al*[12] also pointed out that for patients with increased skin lesions or continuous positive blood culture in monotherapy, the combination of the two drugs for treatment could be considered.

Other studies have proposed that granulocyte recovery is the most important factor for successful treatment of invasive *Fusarium* infection. For patients with agranulocytosis, even if systemic antifungal drugs are given, the fatality rate is still close to 100%[13]. Therefore, colony-stimulating factor (G-CSF) and/or GM-CSF should be given to promote or maintain the recovery of hematopoietic function. Another finding suggests that surgical removal of focal lesions may result in better outcomes in patients with skin or disseminated infections[3].

## CONCLUSION

For children with secondary agranulocytosis after receiving chemotherapy for hematological malignancies, once the typical abnormal skin damage is found, it should be alert to the possibility of *Fusarium* infection, and the key to treatment is early diagnosis, reversal of immunosuppression, and correct antifungal treatment as soon as possible. Voriconazole alone or in combination with polyenes may be the most effective anti-*Fusarium* drugs.

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