

Short Communication

Invasive Fungal Infection Caused by *Geotrichum clavatum* in a Child with Acute Leukemia: First Documented Case from Mainland China

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SUMMARY: Invasive fungal infections are one of the vital complications among acute leukemia patients undergoing induction chemotherapy. Among them, *Geotrichum clavatum* infections present extremely rarely with atypical clinical symptoms which make them difficult to diagnose. In this paper, we report a case of infection caused by *Geotrichum clavatum* in a 10-year old child with acute leukemia, which is the first documented case from mainland China. With underlying childhood leukemia, the child suffered from recurrent bacterial and fungal infection and even underwent abdominal surgery during the treatment. Fortunately, the therapeutic effect was finally achieved by adjusting the treatment program to dual anti-fungal treatment with micafungin and amphotericin B. Information regarding the epidemiological, clinical, and therapeutic features, in this case, shows significant perspectives for anti-fungal treatment for immunocompromised individuals, wherefore the rate of recovery and survival can be achieved.

Invasive fungal infections (IFIs) most frequently affect immunocompromised individuals and present life-threatening challenges (1,2). Among patients with hematological malignancies or undergoing hematopoietic stem cell transplantation (HSCT), the combination of several predisposing conditions increases the risk of IFIs (3–5). Even worse, *Geotrichum clavatum* infections studied in this work present extremely rarely with atypical clinical symptoms which make them difficult to diagnose. Here, we report a case of invasive fungal infection caused by *Geotrichum clavatum* in a child with acute leukemia from mainland China.

A 10-year-old male child was admitted to hospital with a progressively increasing number of hemorrhagic spots on the skin for more than 20 days and diagnosed with “acute T-lymphocytic leukemia L1-type, fusion gene (–)” on hospital day 9. Meanwhile, the patient was treated with pancreatitis-related therapy (vancomycin and sulperazone). On hospital day 22, CCCG-2015 VDCLP chemotherapy was started, and remission was induced using dexamethasone, paclitaxel, vincristine, and daunorubicin. On hospital day 35, the patient developed a fever, sore throat, and tonsillar hyperemia. Thus, Tienam (imipenem/cisplatin; 0.9 g, ivgtt, q8h) was added; however, dry cleft and blood scab occurred on the oral mucosal membrane probably due to the chemotherapy. Then, vancomycin (300,000 U, ivgtt, q6h) and micafungin (50 mg, ivgtt, qd) were scheduled for the treatment of infection. On hospital day 43, the patient

presented with a bloodstream infection (due to *Enterococcus faecium*); thus, vancomycin (300,000 U, ivgtt, q6h) and Tienam (0.9 g, ivgtt, q8h) were constantly used to support anti-bacterial treatment accordingly, combined with micafungin (50 mg, ivgtt, qd) as anti-fungal treatment. Unfortunately, the fever persisted together with rough lung respiratory sounds. A chest computed tomography (CT) scan revealed lightly ground glass-like shadows and mild pulmonary interstitial lesions in both lungs. The result of the galactomannan (GM) test was 1.33 GMI (reference value < 0.5 GMI) and that of the 1,3-β-D-glucan test (G test) was 746 pg/ml (reference value < 60 pg/ml) which indicated severe pulmonary fungal infection. Accordingly, voriconazole (0.15 g, ivgtt, q12h) was added instead of micafungin as anti-fungal treatment. Four days later, a blood culture identified the cause of the fungal infection.

After culturing on blood plates, the fungi presented white and dry cottony colonies with a frosted-glass appearance on the blood plates (Fig. 1). Microscopically, typical hyphae rectangular or rounded at the ends were observed after Gram staining (Fig. 2). The colonies were identified as *G. clavatum* with 99.9% confidence using VITEK MS automatic microbiological mass spectrometry detection system (bioMérieux, Marcy-l'Étoile, France). Drug sensitivity test was also performed using ATB strips (bioMérieux) (Table 1).

On hospital day 58, the patient underwent “exploratory laparotomy + ileal repair + loosening of intestinal conglutination” due to perforation of the digestive tract. It must be noted that the fever persisted and a CT scan of the chest and abdomen revealed liver parenchyma scattered with different sizes of low-density shadows suggestive of hepatic fungal infection. Besides, the GM test result (6.03 GMI) was significantly higher than before (1.33 GMI), so micafungin (100 mg, ivgtt, qd) and voriconazole (0.1 g, ivgtt, q12h) were added as dual anti-fungal therapy. However, the fever still did not

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Fig. 1. (Color online) Macroscopic appearance of *Geotrichum clavatum* in blood plate.



Fig. 2. (Color online) Microscopic appearance of *Geotrichum clavatum* after gram staining.

subside. On hospital day 97, voriconazole was replaced by Feng eriksson (amphotericin B liposomes, 27 mg, ivgtt, qd) with micafungin, after which his fever was subsided. On hospital day 140, chemotherapy was restarted and voriconazole dispersible tablets (200 mg, po, bid) were used as antifungal treatment. Fortunately, there were no leukemic cells and minimal residual disease during the nearly 2 months of a moratorium of chemotherapy during anti-infection treatment.

Unlike *Candida* and *Aspergillus*, there is little information about *G. clavatum*. Currently, only a few relevant studies have reported hematological malignancies as the underlying inducements. A review of the French literature revealed 31 patients with *Geotrichum* infection; the

Table 1. In vitro susceptibility test of *Geotrichum clavatum*

Antibiotics	MIC value (mg/L)	Susceptibility
5-fluorocytosine	<= 4	S
Amphotericin B	<= 0.5	S
Fluconazole	2	S
Itraconazole	<= 0.125	S
Voriconazole	0.125	S

S, susceptible.

majority of them were acute myeloid leukemia patients and the mortality rate was as high as 80% at 60 days after infection (6–8). A review of the Italian literature also demonstrated that in the past 20 years, the mortality rate was 57.1% among the 35 cases of *Geotrichum* infection reported in Italy (9). In recent years, more and more rare pathogenic microorganisms have been identified, benefiting from the application of mass spectrometry technology and large progress in the speed of microbial identification and the scope of strains.

There has always been a dispute regarding when to perform anti-fungal therapy for patients with bone marrow suppression, low immunity, and concomitant bacterial infection during chemotherapy for leukemia. During treatment, in this case, the result of the G test is in good agreement with the general condition and the body temperature which can help clinicians to perform timely adjustments to the anti-fungal treatment schedule. Thus, the G test may be of high value which should be continuously observed in the early stage in *G. clavatum* infection and is in accordance with the view in relevant literature (10).

Currently, fungi are increasingly developing resistance or even cross-resistance, which remain more serious challenges to the prevention and treatment of fungal infection, particularly, invasive fungal infections such as that caused by *G. clavatum*. Voriconazole, amphotericin B and 5-flucytosine are applied for invasive infection with *G. clavatum* since it's naturally resistant to echinocandin (6,11). In this case, monotherapy with voriconazole yielded a poor effect, although susceptibility test showed sensitivity. Only by adjusting to dual-antifungal treatment with micafungin and amphotericin B, was the desired effect finally achieved. Thus far, there is no clear standard treatment or reference for *G. clavatum* infection, and related literature shows a lack of consensus about the effect of voriconazole in the treatment of *G. clavatum* infection. A patient with acute invasive pulmonary *Geotrichum* infection caused by drowning was treated with a combination of caspofungin and voriconazole, but finally died of treatment failure (12). It seems that a higher concentration of amphotericin B may be effective against *G. clavatum* infection because patients with *G. clavatum* infection are more susceptible to invasive organ infection (13) and amphotericin B can accumulate to high concentrations in the lung, liver, and spleen (14). Accordingly, recent guidelines for the treatment of invasive fungal infection strongly recommend amphotericin B for related treatment (11,15). In this case, the infection was finally controlled after the combination of micafungin and amphotericin B. It may also be possible that the patient's primary disease and bacterial

infection were effectively controlled so that the effect of fungal treatment was promoted. Anyway, amphotericin B is considered to be the drug of choice for the treatment of *G. clavatum* infection.

In conclusion, this is the first case report of *Geotrichum* infection in a patient with hematological malignancy from mainland China. Particularly, one should be alert to secondary infection among patients with hematologic diseases during chemotherapy when drugs like echinocandin are used. According to previous literature and the treatment experience with this case, the G test is recommended as an early indicator of suspected diagnostic index as well as an evaluation index of efficacy, and amphotericin B is the first drug of choice for the treatment of *G. clavatum* infection which has some guiding clinical significance for related diagnosis and treatment.

Conflict of interest None to declare.

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