Invasive fungal infection caused by Geotrichum clavatum in an acute leukemia child: first documented case from mainland China

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Invasive fungal infection caused by Geotrichum clavatum in an acute leukemia child: first documented case from mainland China

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**Summary:** Invasive fungal infections (IFIs) are one of the vital complications for acute leukemia patients undergoing induction chemotherapy. Among them, Geotrichum clavatum fungal infections present extremely rare with atypical clinical symptoms which make it difficult to diagnosis. In this paper, we report a case of infection caused by Geotrichum clavatum in a 10-year old acute leukemia child, which is the first documented case from mainland China. With childhood leukemia as the basic disease, the child suffered from repeated bacterial and fungal infection, and even underwent abdominal surgery during the treatment. Fortunately, the therapeutic effect was finally achieved by adjusting treatment program to dual anti-fungal infection with micafungin and amphotericin B. The information of 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 provided.

Invasive fungal infections (IFIs), most frequently affecting immunocompromised individuals, present life-threatening challenges (1, 2). Among patients with haematological malignancies or undergoing haematopoietic stem cell transplan-tation (HSCT), the combination of several predisposing conditions makes them at higher risk of development of IFIs (3-5). Even worse, Geotrichum clavatum fungal infections studied in this work present extremely rare with atypical clinical symptoms which make it difficult to diagnosis. Here we report a case of invasive fungal infection caused by Geotrichum clavatum in an acute leukemia child from mainland China.

A 10-year-old male child was admitted to hospital with progressive increasing of hemorrhagic spots in skin for more than 20 days and diagnosed as "T-acute 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 the 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 (0.9g, ivgtt, q8h) was added, however, dry cleft and blood scab occurred on the oral mucosal membrane which may owe to chemotherapy. Then vancomycin (300 thousand units, ivgtt, q6h) and micafungin (50 mg, ivgtt, qd) were scheduled to treat anti-infection. On hospital day 43, the patient presented as sepsis with a bloodstream infection (enterococcus faecium), so that vancomycin (300 thousand units, IVGTT, q6h) and tienam (0.9g, ivgtt, q8h) were constantly used to support anti-bacterial treatment according, combined with micafungin (50 mg, ivgtt, qd) for anti-fungal treatment. Unfortunately, fever persisted together with rough lung respiratory sounds. The chest CT scan revealed lightly ground glass-like shadow and mild pulmonary interstitial lesion in both lungs, the result of galactomannan test (GM test) was 1.33 GMI (the normal value is <0.5 GMI) and 1,3-β-D-glucan test (G test) was 746 pg/ml (the normal value is <60pg/ml) which indicated severe fungal infection in lungs. Accordingly, voriconazole (0.15g, ivgtt, q12h) was added instead of micafungin for anti-fungal treatment. Four days later, the blood culture caught the culprit of fungal infection.

After cultured on blood plates, the fungi presented white and dry cottony colonies with a frosted-glass appearance on the blood plate (Figure 1). Microscopically, typical hyphae with rectangular or rounded at the ends were observed after gram staining (Figure 2). Besides, the colonies were identified as Geotrichum clavatum (G. clavatum) with a confidence of 99.9% by VITEK MS automatic microbiological mass spectrometry detection system. Furthermore, the drug-sensitivity was tested by French bioMerieux ATB (Table 1).
On hospital day 58, the patient underwent the surgery of "exploration laparotomy + ileal repair + intestines conglutination loosen" due to the perforation of digestive tract. It must be noted that fever still persisted and the CT scan of chest and abdomen revealed the liver parenchyma scattered in different sizes of low-density shadow which may suggested there was fungal infection in liver. Besides, the GM test (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 for dual anti-fungal infection therapy. However, fever was still not remission. 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 for antifungal treatment. Fortunately, there was no leukemic cell and minimal residual disease (MRD) during the nearly 2 months of moratorium of chemotherapy in the period of anti-infection treatment.

Unlike Candida and Aspergillus, there is little information about G. clavatum. Currently, only a few relevant literatures reported that haematological malignancies were the underlying inducements. The French literatures reviewed 31 patients with Geotrichum infection: the majority of them were AML patients and the mortality rate was high to 80% at 60 days after infected (6-8). An Italian literature also demonstrated that in the past 20 years, the mortality rate was 57.1% of the 35 cases with Geotrichum infection in Italy (9). In recent years, more and more rare pathogenic microorganisms have been identified benefited from the application of mass spectrometry technology and it has made large progress in the speed of microbial identification and the scope of strains.

It has always been a dispute that when perform anti-fungal therapy for patients with bone
marrow suppression, low immunity and combination of bacterial infection during chemotherapy of leukemia. In the process of the treatment in this case, the level of G test is in good agreement with the general condition and the body temperature which can help clinicians to timely adjust the antifungal treatment schedule. So that G test may be of high value which should be continuously observed in the early stage in infections of G. clavatum and it is in accordance with the view in relevant literature (10).

Currently, the fungi are increasingly developing resistance or even cross-resistance which remain more serious challenges to the prevention and treatment of fungal infection, especially the invasive fungal infection, such as G. clavatum. Voriconazole, amphotericin B and 5-flucytosine are applied for invasive infection of G. clavatum, since it’s naturally resistant to echinocandin (6, 11). In this case, monotherapy of voriconazole reflected poor effect, although susceptibility test showed sensitive to it. Only by adjusting treatment to dual-antifungal infection with micafungin and amphotericin B, the effect was finally achieved. As so far, there is no clear standard treatment or reference for G. clavatum infection, and related literatures showed there is an argument about the effect of voriconazole in the treatment of G. clavatum infection. The case was that a patient with acute invasive Geotrichum infection in pulmonary caused by drowning was treated with the combination of caspofungin and voroconazole, but finally died of failed treatment (12). It seems higher drug concentration of amphotericin B may be effective to G. clavatum infection, the reason is patients with G. clavatum infection are more likely to get invasive organ infection (13) and amphotericin B can be accumulated to a high drug concentration in lung, liver and spleen (14). Accordingly, the recent guidelines for the treatment of invasive fungal infection strongly recommended amphotericin B be used for related treatment (11, 15). In this case, the infection was
finally controlled after the combination of micafungin and amphotericin B. Maybe there is another possibility 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 first choice for the treatment to G. clavatum infection.

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

Conflict of interest: None to declare.

References


Table 1 *In vitro* susceptibility test of Geotrichum clavatum

Fig. 1 Macroscopic appearance of Geotrichum clavatum in blood plate

Fig. 2 Microscopic appearance of Geotrichum clavatum after gram staining
<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>MIC value (mg/L)</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-fluorocytosine</td>
<td>&lt;=4</td>
<td>S</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>&lt;=0.5</td>
<td>S</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>&lt;=0.125</td>
<td>S</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.125</td>
<td>S</td>
</tr>
</tbody>
</table>

S=susceptible