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Original Article

Candidemia in Patients with Acute Leukemia: Analysis of 7 Years' Experience at a Single Center in China

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Abstract. The study of candidemia in Chinese leukemia patients has been limited. This retrospective study aims to investigate the characteristics and prognostic factors of candidemia among leukemia patients.
From 2009 to 2015, 30 isolates of candidemia were detected in 19 patients with acute leukemia after chemotherapy. The overall incidence of candidemia was 2.12 episodes per 1000 admissions. *Candida tropicalis* was the most common *Candida* species (n = 17; 89.5%). The vast majority of candidal infections are endogeneous. The overall 30-day crude mortality rate was 31.6%. Neutrophil recovery (P = 0.000) and initiation of empiric antifugal treatment before first positive blood culture (P = 0.041) were associated with a significant improvement in overall survival.
Early diagnosis, followed by rapid antifungal treatment remains the cornerstone of successful management. The widespread use of newer antifungal agents as prophylaxis among patients with acute leukemia may result in a decreased candidemia incidence.

Keywords: Candidemia; Acute leukemia; Incidence; Outcome; Prognostic factors; Empirical antifungal treatment.

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Introduction. Candidemia is an infection that can threaten the life of patients with acute leukemia.[1] Most published data about candidemia in China summarized from non-neutropenic patients.[2-4] There are absences of the study of the incidence, microbiologic characteristics, and clinical outcome of candidemia among patients with acute leukemia in China. To clear up these issues, we performed a retrospective research of candidemia in patients with acute leukemia who had been successively treated at our center between 2009 and 2015.

Case Report. This retrospective study reviewed and analyzed 30 isolates of candidaemia involving 19 patients with acute leukemia from January 2009 to December 2015.

Candidemia is defined as the positivity of no less than one blood culture linking to clinical symptoms of bloodstream infection such as hypotension or fever. All patients with acute leukemia and no less than one blood

culture positive for *Candida spp*. were identified. We collected information regarding patient characteristics, type of underlying leukemia, depth of neutropenia, duration of, and recovery from neutropenia, presence of a central venous catheter (CVC) and subsequent removal, prior or concurrent use of antifungal agents and/or broad spectrum antibiotics, laboratory and microbiological data, treatment options and clinical outcomes.

Catheter-associated candidemia was diagnosed when there was no other obvious source of infection, and the identical *Candida spp*. was separated from both the catheter-tip culture and the peripheral blood.[5,6] Patients with neutrophil counts less than 0.5×10^9/L were diagnosed with neutropenia. Prolonged neutropenia was defined as neutropenia lasting for over 12 days before the beginning of fungemia. Neutrophil recovery was defined as the resolution of neutropenia beyond 0.5×10^9/L. Mortality resulting from candidemia was defined as death within 30 days after the initial blood culture under the condition of stable haematological disease and none of the possible reasons for death.

Two patients developed candidemia while being treated with intravenous voriconazole as a prescription for presumed pulmonary fungal disease. Other patients received oral fluconazole as routine antifungal prophylaxis during chemotherapy.

The overall incidence of candidemia was 2.12 episodes per 1000 admissions. Candida tropicalis was the most common Candida species (n=17; 89.5%), followed by Candida albicans (n=2; 10.5%) and one (5%) patient had concomitant bacteremia.

The median age of the population was 38 years old (range: 17 to 64 years), and the sex ratio was roughly equal. The most common underlying disease was acute myeloid leukemia (94.7%). Of the 19 patients with candidemia in this study, 15 (78.9%) had a newly diagnosed disease, 3 (15.8%) were in remission, and one patient (5.31%) had relapsed disease. All patients present with persistent or refractory fever lasted for ten days (range: 2-60 days), and the average peak body temperature was 40°C. The fever may persistent for a long time even after recovery from neutropenia. Erythematous papules appeared on ten (52.6%) patient's skin, mainly on trunk and upper extremities (**Table 1**). No septic shock happened in these patients. Mucosal Candida colonizations (mouth or stools) were observed in eight patients (42.1%) before chemotherapy.

The overwhelming majority of these patients had central venous catheterization (n=18; 94.7%). Before the infection, all patients were neutropenic for an average of 14 days (range: 6 to 20 days). Median time from initiation of chemotherapy to diagnosis of candidaemia was 14 days (range: 9 to 35 days). All patients had received broad-spectrum antibiotics within the preceding eight days (range: 3-20 days) and cephalosporins, imipenem and piperacillin were the most commonly prescribed drugs. Several previously identified risk factors for candidemia were present in our patients.[6] They are listed in **Table 2**.

Table 1. Clinical characteristics.

Characteristics	n=19
Age, year, median (range)	38(17-64)
Gender, no. of men (%)	9(47.4)
Underlying disease, no. (%)	
Acute myeloid leukemia	18(94.7)
Acute lymphoblastic leukemia	1(5.3)
Disease stage, no. (%)	
Induction	15 (78.9)
Consolidation	3 (15.8)
Relapse	1(5.31)
Duration of fever days, median (range)	10(2-60)
Average peak body temperature (°C)	40
Skin rash, no. (%)	10 (52.6%)

Table 2. The frequencies of several potential risk factors for candidemia in the acute leukemia patients (n=19).

Risk factors	n (%)
Induction chemotherapy	15 (78.9)
Mucosal Candida colonizations	8 (42.1)
Damage of the mucocutaneous barrier (mucositis or diarrhea)	12 (63)
Broad spectrum antibiotics Median duration of treatment before first PBC	19 (100) 8 days (range:3-20d)
Neutropenia (<500/mm^3) Median duration before first PBC Median duration after first PBC (only for alive patients)	17 (89) 14 days (range:6-20d) 3 days (range:0-11d)
Central venous catheter	18 (94.7)

PBC: positive blood culture.

6 patients died within 6.5days (range: 5-20 days) of candidemia, leading to a crude mortality of 31.6% and in cases due to Candida tropicalis the mortality was 35.3%, which was similar with the report of Sipsas et al.[1] Almost all surviving patients (12/13; 92.3%) developed a chronic disseminated candidiasis after candidemia.

All isolates of *Candida spp.* were sensitive in vitro to fluconazole, itraconazole, amphotericin B and voriconazole. Susceptibility to echinocandin was not performed as a result of the condition limit. There was no trend of increasing minimum inhibitory concentration observed during the period of 2009-2015.

We further analyzed whether there were any differences in demographic characteristics or risk factors and disease characteristics between those patients who died and those who survived (**Table 3**). We found that the resolution of candidemia was

Table 3. Factors affecting clinical outcome.

Factors	Population data (n=19)		P value
	Survived (n=)	Died (n=)	
Age			
35 year or younger	7	2	0.628
older than 35 year	6	4	
Gender			
Men	7	2	0.628
Women	6	4	
Prolonged neutropenia			
Yes	8	2	0.350
No	5	4	
Neutrophil recovery			
Yes	13	0	0.000
No	0	6	
Initiate empiric antifugal treatment before first PBC			
Yes	10	1	0.041
No	3	5	

PBC: positive blood culture.

associated with neutrophil recovery (P=0.000) and initiation of empiric antifugal treatment before the first positive blood culture (P=0.041). Age, gender, and prolonged neutropenia before the onset were unrelated to the clinical outcome.

As candidemia increases mortality rates by 20–49%, immediate and targeted treatment initiation is necessary. In our study, 11 patients (57.9%) received empirical treatment when a candidal infection was suspected (example, patients present with persist fever had no respondence to broad-spectrum antibacterial antibiotics neither had the manifestation of skin rash), the others begun antifungal treatment after preliminary positive results of blood cultures were reported by microbiology departments. Twelve patients (63.2%) received monotherapy and the other combination therapy. Antifungal treatments were caspofungin (n=5), liposomal amphotericin B (n=5), voriconazole (n=1), fluconazole (n=1), liposomal amphotericin B+voriconazole (n=4), caspofungin+liposomal amphotericin B (n=2) and caspofungin+ voriconazole (n=1). The median duration of intravenous antifungal treatment was 14 days (3–49 days) and 15 days (3–49 days) in all patients and surviving patients respectively.

Fifteen patients' CVC was removed as soon as the first positive blood culture was reported. Results of CVC culture were accessible in these patients and indicated that no patient had an infection of CVC.

Discussion. While the incidence of candidemia seems to be reasonably low in patients with leukemia submitted to intensive chemotherapy, crude and attributable mortality rates have maintained persistently high, and similar to those reported before,[1,7] despite the introductions of new antifungal agents. This study has disclosed several important issues about the epidemiology, manifestations, and therapy of candidemia in Chinese patients, which offers a better understanding and improves the management of this disease.

Candida albicans was the most common *Candida spp.* isolated from general patients or non-neutropenic patients with candidemia in Europe, the US and China.[2,8,9] *C. parapsilosis* and *C. glabrata* were predominant species in hematological patients with candidemia in Europe and US.[1,10] In China, there was an overall increase in isolation of *C. parapsilosis* for cancer patients.[11] However, in our study, *C. tropicalis* (89.5%) was the most common pathogen. This unique epidemiology probably accounts for the predominance of acute leukemia, the majority of neutropenic patients, and all patients treated with cytotoxic agents known to alter the gastrointestinal tract (GIT). In 1986, Walsh et al. have demonstrated the increased invasion of *C. tropicalis* in the GIT of neutropenic patients with mucositis.[12] The physical integrity of the mucous membrane barriers altered by chemotherapy facilitated the spread of infection into the systemic circulation. Therefore, the epidemiology of candidemia varies among different regions and patients.

The mortality rate significantly increases due to the delayed antifungal treatment. Even the delay of 12-24 hours can lead to the twofold increases in crude mortality rate in candidemia.[13] Blood cultures remain the mainstay for the diagnosis of candidemia, but a median incubation time of 2 days (range:1-5 days) was required for species identification and susceptibility in our study, early diagnosis of candidemia is still difficult. In the study, we initiate empirical antifungal treatment due to highly suspicion of candidemia judged by clinicians from symptoms and manifestations in some patients, resulted in a better survival (P=0.041). Among ten patients presented with skin rash, 6 of them suffered from the skin lesions before the preliminary positive results of blood cultures were reported, then early antifungal treatments were initiated. The

presences of skin rash seem to benefit an early diagnosis of this infection. This fact alerts that we should be cautious when we do physical examination screening of fungal infections.

Early CVC removal is strongly recommended by guidelines and considered to be critical to successful treatment in early studies.[14-16] Nevertheless, in our research, the removal of CVCs had no connections with the improvement of clinical outcome, which indicate that the majority of candidal infections are endogenous rather than CVC. It was different from another study in patients with hematologic malignancies.[1] The latest edition of clinical practice guideline for the management of Candidiasis by IDSA (Infectious Diseases Society of America) points out that endogenous sources of candidiasis other than a CVC (example, gastrointestinal tract) predominate in neutropenic patients, so catheter removal should be considered on an individual basis for these patients.[17] This newest suggestion is consistent with our study. However, the fact is that the preservation of CVC has been low. In one study covering children with *C. parapsilosis* complex infections, the preservation of catheter was 33.3% within caspofungin treatment. [18]

From the year 2009 to 2014, three cases of candidemia occurred in our center per year on average. Interestingly, there was no candidemia occurred in the year of 2015, it seems that the widespread use of newer antifungal agents (voriconazole or posaconazole) as prophylaxis among patients with acute leukemia did result in a decreased candidemia incidence. However, further prospective studies and continued surveillance are needed to confirm this hypothesis.

There were several limitations to our study. First, the study was performed only at a single leukemia-chemotherapy center; consequently, it may not reflect local practice patterns and be suitable for transplant submitted patients or other hematologic malignancy. Second, this study was a retrospective investigation. Third, the limited number of cases suffering from candidemia may have compromised the statistical power of the study. However, this study attempts to focus on candidemia in acute leukemia patients receiving chemotherapy and still offers valuable information concerning this issue.

Conclusions. In summary, although the incidence of candidemia seems to be quite low in patients with leukemia receiving intensive chemotherapy as well as the availability of new effective antifungal drugs, its high mortality rate continues to be a crucial problem. Early diagnosis, followed by rapid antifungal treatment, remains the cornerstone of successful management. Catheter removal should be considered on an individual basis. The widespread use of newer antifungal agents as prophylaxis among patients with acute leukemia may result in a decreased candidemia incidence.

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