



Article/Artigo

Fungemia in a university hospital: an epidemiological approach

Fungemia em hospital universitário: uma abordagem epidemiológica

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ABSTRACT

Introduction: Fungemia corresponds to the isolation of fungi in the bloodstream and occurs mostly in immunosuppressed patients. The early diagnosis and treatment of these infections are relevant given the serious threat to the affected patients and possible spread to other organs, often becoming fatal. The growing number of fungemia associated with poor prognosis resulted in this research aiming to diagnose and assess the epidemiological aspects of hematogenous infections by fungi. **Methods:** The study included 58 blood samples collected within a 1-year period, from patients at the *Hospital das Clínicas*, Federal University of Pernambuco, by venipuncture in vacuum tubes. Blood samples were processed for direct examination and culture and identification, conducted by observing the macroscopic and microscopic characteristics, as well as physiological characteristics when necessary. **Results:** Eight (13.8%) episodes of fungemia were identified, accounting for the total sample, and these pathogens were *Candida*, *Histoplasma*, *Trichosporon*, *Cryptococcus*, and a dematiaceous fungus. *C. albicans* was the prevalent species, accounting for 37.5% of the cases. Most affected patients were adult males. There was no predominance for any activity, and the risk of acquired immunodeficiency syndrome was the underlying pathology most often cited. **Conclusions:** The isolation of fungi considered as emergent species, such as *C. membranifaciens* and dematiaceous species, highlights the importance of epidemiological monitoring of cases of fungemia in immunocompromised patients, as the therapy of choice depends on the knowledge of the aetiological agent.

Keywords: Epidemiology. Fungemia. University hospital.

RESUMO

Introdução: Fungemia corresponde ao isolamento de fungos na corrente sanguínea e ocorre, sobretudo, em pacientes imunossuprimidos. O diagnóstico e tratamento precoce destas infecções são relevantes diante da grave ameaça aos pacientes acometidos e possível disseminação via hematogênica para outros órgãos, tornando-se muitas vezes fatal. O crescente número de casos de fungemia associados ao mau prognóstico resultou na realização desta pesquisa que teve por objetivo diagnosticar e avaliar aspectos epidemiológicos das infecções hematogênicas por fungos. **Métodos:** O estudo incluiu 58 amostras de sangue coletadas, durante um ano, de pacientes internados no Hospital das Clínicas da Universidade Federal de Pernambuco, através da punção venosa em tubos a vácuo. As amostras de sangue foram processadas para exame direto e cultura e a identificação, conduzida através da observação das características macroscópicas, microscópicas e quando necessárias fisiológicas. **Resultados:** Oito (13,8%) episódios de fungemia foram identificados, correspondendo ao total das amostras e os agentes etiológicos envolvidos foram *Candida*, *Histoplasma*, *Trichosporon*, *Cryptococcus* e um fungo demáceo. *C. albicans* foi a espécie prevalente com 37,5% dos casos. A maior parte dos pacientes acometidos pertencia ao sexo masculino, na idade adulta. Não houve predominância para nenhuma atividade de risco e a síndrome da imunodeficiência adquirida foi a patologia de base mais citada. **Conclusões:** O isolamento de fungos considerados emergentes como *C. membranifaciens* e espécies demáceas ressaltam a importância do acompanhamento epidemiológico dos casos de fungemia em imunocomprometidos, uma vez que a escolha terapêutica depende do conhecimento do agente etiológico.

Palavras-chaves: Epidemiologia. Fungemia. Hospital universitário.

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INTRODUCTION

In recent years, there was a marked increase in the number of serious infections caused by pathogenic fungi and those traditionally considered non-pathogenic. Infections caused by these organisms usually occur in patients with impaired immune defense, suffering from cancer, with acquired immunodeficiency syndrome (AIDS), or who received immunosuppressive therapy, had disruptions of the normal barriers, or experienced changes in normal microbiota¹.

Advances in medicine have led to prolonged survival of immunocompromised patients and as well as the development opportunistic fungal infections. Among these infections, fungemia corresponds to the presence of fungi in the bloodstream, whose incidence has risen in recent decades. The presence of viable microorganisms in the bloodstream suggests active infection in tissues, and the patient's recovery may depend on early identification and isolation of the aetiological agent^{2,3}.

Fungemia or hematogenous fungal infections represent a serious health problem, involving hospitalized patients with predisposing conditions leading to a high mortality rate^{4,5}.

The clinical presentation is nonspecific, and fever is the most common one^{2,6}, which makes the diagnosis of fungemia a challenge, as blood cultures are positive in less than 50% of cases^{6,7}. Thus, the diagnosis is usually late in the course of the infection or even during necropsy⁴.

Yeasts have been increasingly present as aetiological agents of fungemia, including *Candida albicans* and other species such as *Candida non-albicans*⁵. Nevertheless, other fungi, such as *Histoplasma capsulatum*, may also be involved. Differential patterns of species distribution have not been fully elucidated and may be closely related to the potential virulence of these microorganisms⁸.

The early diagnosis and treatment of these fungemias are relevant given the serious threat to immunocompromised patients and possible spread, hematogenously, to deeper organs, often becoming

fatal. An appropriate management through clinical and laboratorial diagnosis may be effective with a satisfactory global health benefit⁹.

The growing number of fungemia associated with poor prognosis led to this study aiming to diagnose and evaluate the epidemiological aspects of hematogenous infections by fungi.

METHODS

This study was conducted in hospitalized patients at the Sector of Infectious and Parasitic Diseases of the *Hospital das Clínicas* (Federal University of Pernambuco), and the procedures performed are in accordance with the ethical standards of the human experimentation committee of the Center for Health Sciences, Federal University of Pernambuco, Brazil. Patients' personal data were registered such as age, sex, occupation, and underlying disease. Three venous blood samples were aseptically collected in consecutive days by venipuncture into Vacutainer® tubes using EDTA anticoagulant. This is an unusual technique for detection of fungemia introduced to facilitate the diagnosis through direct examination, which is not possible to perform using the standard methods. The samples were processed by usual methods (direct examination and isolation in culture) for mycological diagnosis at the Medical Mycology Laboratory, Federal University of Pernambuco.

Direct examination of clinical specimens was performed without clarification, as well as Giemsa staining and Nankin. Aliquots of 2mL of total blood were plated in the form of striations on Sabouraud dextrose agar broth and brain heart infusion, both added with chloramphenicol (Difco Laboratories) incubated at 30°C and 37°C in an aerobic atmosphere for 20 days. Pure cultures were transferred to the surface of Sabouraud dextrose agar plus yeast extract for the taxonomic identification of the etiologic agents^{10, 11}.

The identification was conducted on the basis of their morphophysiological properties and biochemical tests, including auxanogram, zimogram, acid, and urease production according to Barnett¹² and De Hoog¹⁰. The identification was also done by the automated system VITEK 120 (bioMerieux).

RESULTS

In a period of 1 year, 58 blood samples from inpatients with clinical suspicion of fungal blood infection and with a compromised immune system were analyzed. A total of eight episodes of fungemia were identified during this period (March 2009 to March 2010). After completion of the mycological laboratory diagnosis with direct examination and culture, based on the observation of macroscopic, microscopic, and physiological characteristics, fungemia aetiological agent yeasts of the genera *Trichosporon*, *Candida*, and *Cryptococcus* as well as a representative dimorphic *Histoplasma capsulatum* and a representative of dematiaceous filamentous fungi were identified. The incidence of patients with fungemia was 13.8%, and the aetiological agents are shown in **Table 1**.

The age of the eight patients with fungemia, ranged from 24 to 55 years (mean: 36.3 years), predominantly (25.8%) in men. Their occupations varied from being a housewife, bricklayer, hairdresser, truck driver, and teacher, with no predominance for any risky activity.

From the total number of patients analyzed, 31 (53.4%) had human immunodeficiency virus (HIV), and AIDS was the most frequent underlying pathology cited among the affected patients with fungemia, corresponding to five (62.5%) cases, followed by lupus erythematosus, malignant tumors, and *diabetes mellitus*, with one case each. Among the patients with AIDS, two (40%) were injecting drug users, four (80%) were homosexual, and one (20%) was heterosexual.

Based on clinical evaluation, all patients with fungemia were anemic with febrile conditions; one (12.5%) with pancytopenia; six (75%) with vomiting, diarrhea, and respiratory problems; and two (25%) with cutaneous rash.

After mycological diagnosis, four patients received amphotericin B (total dose of 400mg to 2g), which is considered the drug of choice for the treatment of systemic mycoses. Three patients died even before starting this treatment. In one of the patient, the treatment was not instituted for abandonment of monitoring. From those who received the treatment, three had an initial good response, receiving maintenance therapy after symptoms remission, with amphotericin B (1mg/kg/dose once a week) or itraconazole daily. One patient died during hospitalization and treatment.

TABLE 1 - Distribution of causative agents of fungaemia according to gender, age, underlying pathology and occupation of the patients.

Fungaemia agent	Gender	Age	Underlying pathology	Occupation
<i>Candida albicans</i>	female	25	malignant tumors	no occupation
<i>Candida albicans</i>	male	33	AIDS	hairdresser
<i>Candida albicans</i>	male	55	AIDS	bricklayer
<i>Candida membranifaciens</i>	female	39	AIDS	housewife
<i>Cryptococcus neoformans</i>	male	24	AIDS	hairdresser
Dematiaceous fungi	male	35	<i>diabetes mellitus</i>	teacher
<i>Histoplasma capsulatum</i>	female	32	lupus erythematosus	no occupation
<i>Trichosporon</i> sp.	male	48	AIDS	truck driver

AIDS: acquired immune deficiency syndrome.

DISCUSSION

In this group of patients diagnosed with fungemia, treatment was started only after laboratorial diagnosis. Early detection of risk factors for the development of fungemia, such as administration of broad-spectrum antibiotics, use of multiple lumen catheters, mechanical ventilation, parenteral nutrition, and colonization fungal, has led to empirical treatment to reduce the high mortality rate associated with fungal infections¹³. Other factors cited as underlying conditions are malignant diseases, use of corticosteroids, cancer chemotherapy, radiation, malnutrition, and advanced age; they are identified as adjuvant agents in the onset of fungemia^{5,7}.

Fungemia generally induces fever, myalgia, and, possibly, a skin rash. Tests for detecting microorganisms in blood cultures are needed in cases of renal involvement, osteoarticular lesions, endocarditis, meningitis, hypotension and multiple organ failure and other factors¹⁴.

In this study, the majority of the diagnosed cases of fungemia had *Candida* species as the main agent, and such results are similar to the findings of other studies, suggesting this genus as primarily responsible for cases of fungemia in immunosuppressed patients^{2,15}.

It was established that the genus *Candida* is principally involved in the onset of nosocomial infections, where *C. albicans* fungemia is cited as the main cause, although there are increasing reports of blood infections caused by other species of *Candida* non-*albicans* and emergent fungi species^{16,17}. Colombo⁵ showed the detection of 145 candidemia in six hospitals in Brazil the prevalence of *C. non-albicans* species in 63% of cases, *C. parapsilosis* and *C. tropicalis*, the predominant, although the last three decades in American teaching hospitals, *C. albicans* species has been responsible for more than six-fold increase in the frequency of fungemia by this yeast^{18,19}.

In this research, we isolated *C. membranifaciens* as the causative agent of fungemia. Franci and Pecile²⁰ also reported a case caused by this species in cancer patients. *C. membranifaciens* has traditionally been considered non-pathogenic, and this is the first reported case of systemic infection in a patient with AIDS. Additionally, the incidence of dematiaceous fungi isolated from blood of patients with *diabetes mellitus* has rarely been reported.

During the mycological laboratorial diagnosis, it is possible to detect fungemia caused by *C. neoformans*, *Trichosporon*, *H. capsulatum*, and dematiaceous fungi. According to the National STD/AIDS of the Ministry of Health, from 1980 to 2002, 6% of opportunistic infections in HIV-positive patients were caused by *C. neoformans*. Considering the opportunistic fungal infections that affect patients with HIV worldwide, cryptococcosis is the second-most common²¹.

The association of histoplasmosis and HIV is frequently found where the mycosis is endemic, with prevalence ranging between 2% and 30%, based on the studied region. In our research, we observed the involvement of *H. capsulatum* in homosexual patient, 32 with HIV. In most cases, latent foci of histoplasmosis, may culminate in disseminated form.^{14,22} According to Borges²², 18 cases of histoplasmosis occurred in immunosuppressed patients, and 17 had AIDS, mostly males.

We had a case of *Trichosporon* fungemia, which is considered an emerging pathogen in disseminated infections. The clinical picture

of infection by this yeast is nonspecific and very poor prognosis^{23,24}. In a study conducted by Di Bonaventura²³, it was shown that biofilm formation by *Trichosporon* spp explains the persistence of infection despite *in vitro* susceptibility to antifungal agents.

It is considered that early administration of amphotericin B can result in clinical improvement for fungal infections. However, when patients are immunocompromised, there may be resistance to this drug *in vivo*, which explains the high rates of mortality in this population²⁴. In our work, amphotericin B was prescribed with good results.

In conclusion, our data show that the species *C. albicans*, *C. non-albicans*, *H. capsulatum*, and *C. neoformans* remain the leading aethiologic agents causing fungemia, although other emergent species may also be involved such as *Trichosporon*. AIDS remains the most common underlying disease among males. Thus, completion of the mycological laboratory diagnosis in immunosuppressed patients remains essential in guiding an accurate and early treatment to cure the infection.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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