BRIEF REPORT

CHARACTERISTICS OF FUNGEMIAS IN A PERUVIAN REFERRAL CENTER: 5-YEAR RETROSPECTIVE ANALYSIS

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ABSTRACT

Retrospective descriptive study carried out to determine the characteristics of fungemias in 285 cancer patients hospitalized from 2012 to 2016 at the Instituto Nacional de Enfermedades Neoplásicas (INEN). Demographic, clinical and microbiological information was evaluated. Fungemia by *C. albicans* predominated in patients with solid tumors and without neutropenia, while those caused by *C. tropicalis* predominated in patients with hematological neoplasia and neutropenia. *C. tropicalis* was the agent isolated in most cases (47.0%). Fungemia increases over time in patients without neutropenia. Fungemia caused by *C. albicans* increases with age in patients with solid tumors without neutropenia. It is concluded that fungemias are mainly caused by *C. tropicalis* in patients with hematological neoplasia with neutropenia and by *C. albicans* in patients with solid tumors without neutropenia. In addition, fungemia in patients without neutropenia increases over time; and those caused by *C. albicans* increase with age in patients with solid tumors without neutropenia.

Keywords: Epidemiology; Trends; Etiology; Invasive Mycoses; Candidemia; Cancer Care Facilities (source: MeSH NLM).

INTRODUCTION

Fungemias are the most frequent invasive mycosis, with high morbidity and mortality, and have increased due to the growing number of immunocompromised patients, especially oncological cases [1,2]. Fungemias vary according to certain demographic (age, gender, and geographical region) and clinical (underlying diseases, the primary focus of infection, and state of neutropenia) characteristics. Besides, etiology plays an important role in their occurrence [3,4].

Within the varied etiology of fungemias, we find filamentous fungi and yeast-like fungi; which are the most predominant. Although *Candida albicans* (*C. albicans*) has long been the most common species to be isolated, other *Candida* species and yeasts other than *Candida* appear to emerge and displace *C. albicans* [5,6]. Besides, these pathogens have different sensitivity profiles to antifungal agents [7]. Therefore, the associated epidemiology, and etiology have implications for the therapeutic management and outcome of fungemias. The demographic, clinical and etiological characteristics of fungi have been poorly described in our population. Knowing the characteristics of fungemias in hospitals will improve control mechanisms and treatment for these invasive mycoses.

The objective of this study is to determine the characteristics of fungemias in oncology patients hospitalized from 2012 to 2016 at the Instituto Nacional de Enfermedades Neoplásicas (INEN) in Peru.

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THE STUDY

A retrospective descriptive study of fungemia cases diagnosed in the microbiology laboratory of INEN between January 2012 and December 2016. The information was obtained from the registry of the Microbiology Laboratory and the INEN computer system. All cases in which the etiological agent could be identified were included. Duplicate isolates corresponding to the same patient were excluded from the study.

Fungemia diagnosis was made by blood cultures processed in the automated system BD Bactec™ Fx. The yeast identification was made by morphological analysis, according to Dalmau's technique in rice extract agar; and by biochemical analysis, according to the chromogenic characteristics in CHROMagar medium and the characteristics of carbohydrate assimilation in the commercial API 20C AUX system (bioMérieux) [8]. Filamentous fungi were identified by their macroscopic and microscopic characteristics [9].

Fungemia was defined as the isolation of fungi from blood or bone marrow [10]. Additionally, demographic characteristics, such as age (age group) and gender were evaluated; as well as clinical characteristics, such as medical department, type of neoplasia, oncological diagnosis and state of neutropenia defined as count <1000 neutrophils/mm^3 [11]. Microbiological characteristics were also evaluated, such as etiology (grouped into *C. albicans*, non albicans *Candida,* and other yeasts and filamentous fungi) and the sown sample.

Descriptive statistics were used, the results were summarized in frequencies and percentages, and in line and bar charts to evaluate the variables distribution. This study was performed with data from the registry of the microbiology laboratory and the computer system of the INEN, so it does not represent any risk for patients. The study was evaluated and approved by the INEN Research Committee.

KEY MESSAGES

Motivation for the study: Fungemias have high morbidity and mortality rates in oncological patients, so it is necessary to know their epidemiological characteristics.

Main findings: Fungemias by *C. albicans* predominated in patients with solid tumors and without neutropenia. Fungemias caused by *C. tropicalis* predominated in patients with hematological neoplasias and with neutropenia. *C. tropicalis* was the most frequent etiological agent (47.0%). Fungemias in patients without neutropenia increased with time and those caused by *C. albicans* in solid tumors without neutropenia increased with age.

Implications: Knowledge of the epidemiological characteristics in our population will improve therapy and control of these invasive mycoses.

RESULTS

During the five studied years, 36,923 blood cultures were performed, from which 285 (0.8%) turned out to be cases of fungemia, which increased over time. In 2012, 5,814 blood cultures were taken, and 34 cases were found (0.7%). In 2013, 6,400 blood cultures were taken, and 41 cases were found (0.6%). In 2014, 7,438 blood cultures were taken, and 59 cases were found (0.8%). In 2015, 7,861 blood cultures were taken, and 71 cases were found (0.9%). Finally, in 2016, 9,410 blood cultures were taken, and 80 cases (0.9%) were found to be fungemias.

Fungemias were more frequent in the age group from 0 to 19 years old (27.4%) and in the female population (54.4%). From the total, 56.5% patients had neutropenia; 64.6%, hematological neoplasias; 31.9%, diagnosed with acute lymphocytic leukemia; and 10.2% was from the Abdomen Medical Department. The demographic and clinical characteristics of the patients with fungemias distributed by etiology are described in Table 1.

Compared to the fungemias caused by non *albicans Candida*, those caused by *C. albicans* had a higher prevalence rate in patients from the Abdomen Medical Department (17.2% versus 8.0%). When Candida species were analyzed in these patients, it was found that *C. albicans* alone was more frequent than *C. tropicalis* (17.2% vs. 5.2%).

Fungemia by *C. albicans* (54.0%) was more frequent than those caused by non albicans Candida (31.6%) and other yeasts (14.8%) in patients with solid tumor. On the analysis of hematological neoplasms and *Candida* species, *C. tropicalis* was found to be more frequent than *C. albicans* (77.6% versus 46.0%).

C. albicans was more frequently isolated than non *albicans* in patients with non-Hodgkin's lymphoma (20.3% vs. 9.1%) and genitourinary tumor (18.8% vs. 8.6%). When non-Hodgkin's lymphoma and *Candida* species were analyzed, *C. albicans* alone was more frequent than *C. glabrata* (20.3% vs. 0.0%). In genitourinary tumors, *C. albicans* was more frequent than *C. tropicalis* (18.8% versus 6.7%).

In contrast, there was a lower proportion of *C. albicans* (10.9%) compared to non albicans *Candida* (37.4%) and other yeasts (44.5%) in patients with acute lymphocytic leukemia (ALL). When ALL and *Candida* species were analyzed, it was found that *C. albicans* was less frequent than

Table 1. Demographic and clinical characteristics of patients with fungemias distributed by etiology (285 cases).

Variables	*C. albicans*	No-*albicans C.*	Other yeasts	Filamentous fungi	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Age group (years)					
0-19	13 (20.3)	52 (27.8)	11 (40.8)	2 (28.6)	78 (27.4)
20-39	12 (18.8)	47 (25.1)	5 (18.5)	2 (28.6)	66 (23.1)
40-59	20 (31.2)	49 (26.2)	5 (18.5)	2 (28.6)	76 (26.7)
60+	19 (29.7)	39 (20.9)	6 (22.2)	1 (14.2)	65 (22.8)
Gender					
Male	30 (46.9)	80 (42.8)	16 (59.3)	4 (57.1)	130 (45.6)
Female	34 (53.1)	107 (57.2)	11 (40.7)	3 (42.9)	155 (54.4)
Medical department					
Medicine	27 (42.2)	120 (64.2)	14 (51.9)	5 (71.4)	166 (58.3)
Pediatrics	8 (12.5)	30 (16.0)	8 (29.6)	0 (0.0)	46 (16.1)
Abdomen	11 (17.2)	15 (8.0)	3 (11.1)	0 (0.0)	29 (10.2)
Others [a]	18 (28.1)	22 (11.8)	2 (7.4)	2 (28.6)	44(15.4)
Type of neoplasia					
Solid tumor	34 (54.0)	59 (31.6)	4 (14.8)	3 (42.9)	100 (35.1)
Hematological neoplasia	29 (46.0)	128 (68.4)	23 (85.2)	4 (57.1)	184 (64.6)
Oncological diagnosis					
Acute myeloid leukemia	5 (7.8)	32 (17.1)	4 (14.8)	1 (14.3)	42 (14.8)
Acute lymphocytic leukemia	7 (10.9)	70 (37.4)	12 (44.5)	2 (28.6)	91 (31.9)
Non-Hodgkin's lymphoma	13 (20.3)	17 (9.1)	3 (11.1)	1 (14.3)	34 (11.9)
Gastrointestinal tumor	14 (21.9)	31 (16.6)	2 (7.4)	1 (14.3)	48 (16.9)
Genitourinary tumor	12 (18.8)	16 (8.6)	0 (0.0)	2 (28.6)	30 (10.5)
Others [b]	13 (20.3)	21 (11.2)	6 (22.2)	0 (0.0)	40 (14.0)
Neutropenia					
No	46 (71.9)	64 (34.2)	11 (40.7)	3 (42.9)	124 (43.5)
Yes	18 (28.1)	123 (65.8)	16 (59.3)	4 (57.1)	161 (56.5)

[a] Urology, Gynecology, Intensive Care Unit, Head and Neck surgery, Neurosurgery, Thorax, Breast and Tissues, Orthopedics, Nephrology, Intensive Care Unit
[b] Chronic myeloid leukemia, chronic lymphocytic leukemia, Hodgkin's lymphoma, multiple myeloma, head and neck tumor, lung tumor, liver tumor, skin tumor, osteosarcoma, Langerhans cell histiocytosis, acute unspecified cell leukemia, hemophagocytic syndrome, undiagnosed.

C. tropicalis (10.9% vs. 44.8%) and other *Candidas* (10.9% vs. 35.3%).

Fungemias by *C. albicans* had a higher proportion (71.9%) than those caused by non albicans *Candida* (34.2%) and other yeasts (40.7%) in patients without neutropenia. When these patients and the *Candida* species were analyzed, *C. albicans* was more frequent than *C. tropicalis* (71.9% vs. 26.1%) and other *Candidas* (71.9% vs. 29.4%).

Furthermore, when analyzing the type of neoplasia and the degree of neutropenia, it was found that patients with solid tumors without neutropenia were more frequent than those having neutropenia (67.5% vs 10.6%).

Candidemia (251 cases) represented 88.1% of the fungemias, and non albicans *Candida* was isolated in 65.6% (187) of the cases. *C. tropicalis* was isolated in most cases at 47.0% (134 cases). Other yeasts were isolated in 9.5% (27) of the cases and filamentous fungi in 2.5% (7) of the cases (Table 2).

Non-*albicans Candida* predominated during the five reviewed years, although it had a decrease in frequency, from 73.5% in 2012 to 60.6% in 2015. The frequency of C. albicans increased from 14.7% in 2012 to 31.0% in 2015. Other yeasts and filamentous fungi remained below 14.0% and 4.0%, respectively (Figure 1).

Variations in fungemia frequency and in the degree of neutropenia were found and were related to the time elapsed. Fungicides in patients without neutropenia increased from 23.5% in 2012 to 55.0% in 2016. In addition, we analyzed the variation in the frequency of fungemias and the type of neoplasia and did not find a sustained increase over time.

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Fungemia frequencies varied in relation with age, according to the type of neoplasia, oncological diagnosis, degree of neutropenia, and etiology. Fungemias in patients with solid tumors and gastrointestinal cancer increased with age, from 17.9% in the 0-19 years age group to 75.4% in the 60+ years age group, and from 2.5% in the 0-19 years age group to 50.8% in the 60+ years age group, respectively. Similarly, fungemias in patients without neutropenia increased from 34.6% in the 0-19 years age group to 81.5% in the 60+ years age group. Finally, fungemias by *C. albicans* increased from 16.7% in the 0-19 years age group to 29.2% in the 60 or more years age group (Figure 2)

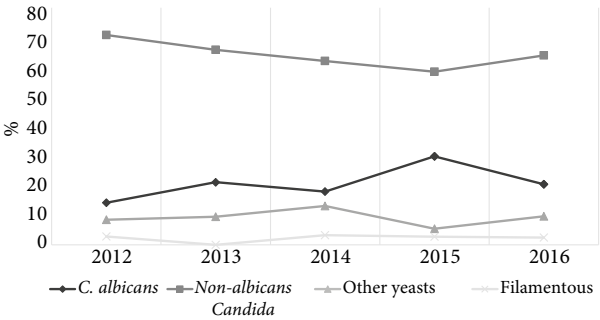

Figure 1. Percentage distribution of the grouped etiology of fungemias, from 2012 to 2016

DISCUSSION

The type of neoplasia and the degree of neutropenia seem to be related to the etiology of fungemias. The predominance of fungemias by *C. albicans* in patients with solid tumors and the predominance of fungemias by non-*albicans Candida,* (mainly *C. tropicalis* in ALL) and other yeasts in hematological neoplasias may be due to the origin of the infection.

Table 2. Distribution by fungemias etiology (285 cases).

Etiological agent	n	%
Yeasts		
C. albicans	64	22.5
C. tropicalis	134	47.0
C. parapsilosis	18	6.3
C. glabrata	18	6.3
C. krusei	4	1.4
C. guillermondi	5	1.7
C. lusitaniae	3	1.1
Otras Candida[s a]	5	1.7
C. neoformans	6	2.1
Cryptococcus sp.	4	1.4
T. asahii	6	2.1
Trichosporon sp.	4	1.4
Rhodotorula spp.	4	1.4
Otras levaduras[b]	3	1.1
Filamentous fungi		
Fusarium spp.	4	1.4
Acremonium spp.	3	1.1

[a] *C. famata* (n=1), *C. kefyr* (n=1), *C. zeylanoides* (n=1), *Candida sp.* (n=2)
[b] *Khodamoeba ohmeri* (n=2), *Geotrichum spp.* (n=1)

In solid tumors the origin is mainly endogenous, while in hematological neoplasias the origin would be by non-commensal yeasts [12,13]. Likewise, we find a higher frequency of *C. albicans* in genitourinary and abdominal tumors since *C. albicans* is common in these anatomical regions and causes postoperative complications in abdominal surgeries [14,15].

On the other hand, the high frequency of fungemia by *C. albicans* in non-neutropenic patients and by *C. tropicalis* in neutropenic patients can be explained by the relationship between the type of neoplasia and the degree of neutropenia. Fungemia by *C. albicans* occurs in solid tumors without neutropenia, while *C. tropicalis* appears in hematological neoplasias with neutropenia. Some studies show that non-neutropenia is more frequent in patients with solid tumors than in hematological neoplasias [16,17].

The diversity in the type and frequency of fungemias etiology determines the appropriate antifungal therapy. Candidemias were the most frequent fungemias, with predominance of non albicans *Candida*, being *C. tropicalis* the most isolated one. The high frequency of the non-*albicans Candida*, *C. tropicalis*, as the cause for fungemias has already been described in some studies of our region [18,19]. The possible association between cancer and fungemias by *C. tropicalis* may explain its etiological predominance [19].

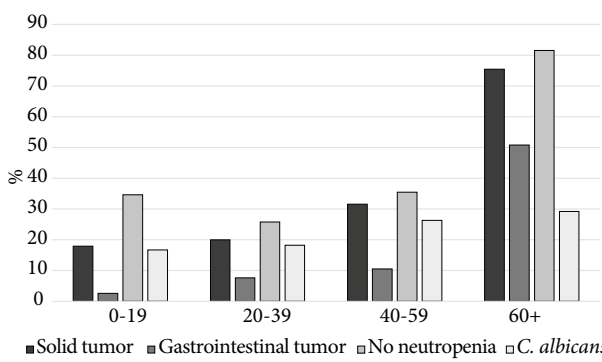

Figure 2. Proportion of fungemia according to clinical characteristics and age group.

Possible trends were found, and these appear to be clinically correlated, but further evaluation is needed. The increase in fungemia duration in patients without neutropenia would indicate that neutropenia is less necessary for the development of these invasive mycoses. This increase would not be due to an increase in solid tumors as these remain invariable over time. The continuous increase of fungemia cases according to age in patients with solid tumors (particularly gastrointestinal tumors) may be due to characteristics of these neoplasias. Patients with solid tumors are older than those with hematological neoplasias [20].

Finally, the continuous increasing number of fungemias by *C. albicans* in patients without neutropenia, which increases with age, can be explained by the relationship between these two characteristics and solid tumors, something already described in previous paragraphs. Solid tumors are more frequent in older adults and, at the same time, are related to fungemias by *C. albicans* and not having neutropenia.

Our study had some limitations, such as data retrospectively collected and the small sample for some categories of the variables considered, which prevented an inferential analysis. Also, fungal identification was performed at the phenotypic level, although molecular techniques provide a more reliable identification, they are expensive, complex, and not very applicable to hospital laboratories.

In conclusion, our findings suggest that fungemias are predominantly caused by *C. tropicalis*, mainly in patients with hematological neoplasias with neutropenia, while fungemias by *C. albicans* predominate in patients with solid tumors without neutropenia. Besides, as years go by, prevalence of fungemias increase in patients without neutropenia. As age increases, prevalence of fungemias by *C. albicans* increase in patients with solid tumors without neutropenia.

Future studies are advised to assess the antifungal sensitivity of isolates, the association with risk factors for fungemia occurrence and the outcome of fungemias. This will allow us to understand the current scenario of fungemias in cancer patients and to take appropriate control and treatment measures.

Authorship contributions: FV participated in the study design, the development of the working protocol, the processing and analysis of the results, and the final writing of the manuscript. JV and KC participated in the study design, and data collection and processing. EB and SM participated in the study design and data collection. SO and IC participated in the study design, the data collection, and processed and analyzed the results. All authors reviewed and approved the final version of the manuscript.

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