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Rate, Risk Factors, and Outcomes of Invasive Fungal Infections in Patients with Hematologic Malignancies

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ABSTRACT

Background: Invasive fungal infections (IFIs) are a significant cause of mortality and morbidity in patients with hematological malignancies. Given the considerable prevalence and consequences of IFIs, hence revealing the exact cause of fungal infections, their rate, associated risk factors, and complications could contribute to reducing both financial and life costs, choosing targeted antifungal treatment, and avoiding unnecessary toxic treatments in individuals who are not suffering from mycoses.

Materials and Methods: This prospective cross-sectional study was conducted in the first semester of 2019. All patients with hematologic malignancies (HM) admitted to Dr. Shariati Hospital were studied. Only those with probable/proven IFIs defined according to the last update of EORTC/MSG criteria were included in the study. The demographic and clinical data were recorded from the hospital information registration system using a questionnaire. Statistical analysis was performed using SPSS software version 24.

Results: Out of 1109 HM patients hospitalized during the study period, 67 (6.04%) IFIs were diagnosed. Of these, 57 (85.04%) were aspergillosis, 7 (10.4%) were mucormycosis, and 3 patients developed other fungal infections. Males constituted 67.2% of the entire IFI population. The mean±SD age of the samples was 43.16 ± 13.8 years. The most common type of malignancy was AML. Lung imaging showed lesions associated with fungal infections in 52 cases (77.6%), with multiple nodules as the most prevalent pattern being observed in 64.2% of cases. Sinus involvement was evidenced in the PNS CT scan of 46 (68.6%) patients. The attributable mortality rate for IFIs was 62.7%. Both the types of IFI and malignancies had no significant relationship with the outcome of patients. Central venous catheter, mucositis, and antibiotic use were the most frequent risk factors.

Conclusion: IFI represents a frequent complication for HM patients with high mortality. *Aspergillus* species are the predominant etiology in these settings. Considering our results, in high-risk patients, manifestations of warning signs in the sinus and lungs, which would not be cleared despite receiving antibiotics, should raise the possibility of IFIs.

Keywords: Hematologic malignancy; Invasive fungal infection; Aspergillosis; AML; Risk factors

INTRODUCTION

One of the most common problems seen in patients with hematologic malignancies (HMs) is their susceptibility to opportunistic infections, including fungal infections, which have been reported in up to 18.1% of those hospitalized in this setting[1], and invasive fungal infections (IFIs) are important causes of morbidity and mortality in these patients. Chemotherapy and ensuing neutropenia disrupt one of the main arms of innate immune system (e.g. phagocytosis).

Defects in the phagocytic process are leading causes of IFIs in acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), and hairy cell leukemia (HCL). Moreover, lack of T cells as well as T cell and macrophage dysfunction predispose to IFIs in leukemia, T cell lymphoma, and Hodgkin's disease[2]. Among yeasts, *Candida* spp. are considered the most common causes of IFIs. The prevalence of invasive candidiasis (IC) in patients with HM who have not received prophylaxis is reported to be 8-24%. *Candida* species are part of normal flora of skin, mouth, intestines, and vagina. Mucosal damage in patients undergoing chemotherapy and neutropenia can lead to systemic infection by these fungi. In the induction phase of AML chemotherapy, the main risk factor of IC is mucosal and gastrointestinal damage.

After *Candida*, the most common yeast causing IFIs is Cryptococcus species which is mainly manifested as cryptococcal meningitis [3, 4]. In patients with AML, not receiving mold-active prophylaxis, the prevalence of invasive aspergillosis (IA) is estimated to be between 5-10%. The leading cause of IA is multiple chemotherapies in persistent or progressive AML[5, 6]. Mucormycosis is the second most common cause of invasive mold infections (IMIs) in patients with HMs. Mucormycosis can cause severe infections of the sinuses, lungs, and brain or some disseminate to other parts of the body[7, 8]. In general, the risk of IFIs in patients with acute leukemia and bone marrow transplant recipients is higher than in patients with chronic leukemia, lymphoma, and multiple myeloma. As a result, the rate of morbidity and mortality in patients with acute leukemia and bone marrow transplant recipients is higher compared to chronic leukemia, lymphoma, and multiple myeloma[9,10]. Candidemia and IA are associated with poor prognosis and a mortality rate of 33% and 42%, respectively. Mucormycosis has the worst prognosis among IFIs, with a mortality rate of 64% [11-13].

Considering the significant prevalence and consequences of IFIs in patients with HM imposing severe human and financial costs on society, guiding in choosing antifungal prophylaxis regimen and targeted therapy, revealing the rate of IFIs in hematology setting is issue of great importance. Therefore, this study was conducted to assess the risk factors, rate, and consequences of IFIs in patients with HMs.

MTERIALS AND METHODS

This prospective cross-sectional study was conducted in the hematology ward of Dr. Shariati Hospital, a tertiary referral center affiliated to Tehran University of Medical Sciences (TUMS), Tehran, Iran, between April 1, 2019, and September 20, 2019. The study population targeted all adult patients (aged over 16 years) with HM admitted to the hematology wards during the survey period. All documented episodes of IFI were included. Patients with solid organ malignancies, outpatient cases, concomitant HMs, and instances such as HIV, bone marrow transplant recipients, solid organ transplant recipients, patients with underlying rheumatic diseases who received high doses of corticosteroids, autoimmune diseases treated with corticosteroids or immunosuppressive drugs, and *either inherent* genetic *diseases* or *acquired conditions* leading to immunodeficiency were excluded from the study.

Upon suspicion of IFI, the diagnostic works up, including imaging (e.g. computed tomography (CT) scans), blood cultures, pharyngeal swab, serological tests for IFI, skin, nasal or sinus biopsy, and bronchoalveolar lavage for mycological assay were considered according to the site of involvement. The consensus criteria proposed by the EORTC/ MSG were used to define IFI. Nonetheless, analysis was restricted to IFI classified as *proven* or *probable*; those with possible IFI were not considered in our investigation[14]. Regarding the identification of fungal isolates, morphological features were applied. The demographic and clinical data were recorded from the hospital information registration system using a

questionnaire. Survival at 90 days post-diagnosis was considered.

Data analysis

Statistical analysis was conducted using SPSS software version 24 (Statistical Package for the Social Sciences, Chicago, IL). Frequency Tables, Chi-square, and independent t-tests were employed for quantitative variables, while Fisher and Chi-square tests were utilized for qualitative variables. A significance level of less than 5% ($p < 0.05$) was considered statistically significant.

Ethical statement

Ethical approval for this study was obtained from the Ethics Committee of Tehran University of Medical Sciences on December 6, 2017 (IR.TUMS.MEDICINE.REC.398.738).

RESULTS

During the study period, a total of 1109 patients with HM were admitted to the hematology wards and 67 (6.04%) IFI cases were documented. Molds caused the majority of cases being detected in 66/67 (98.5%) cases, while only one yeast infection was detected (1.5%). Aspergillosis was the most common IFI (57/67, 85.01%). It accounted for 86.4% of mold infections analyzed, followed by mucormycosis (7/67, 10.6%), fusariosis (2/67, 3%) and candidiasis (1/67, 1.5%).

The diagnosis of aspergillosis was categorized as probable in 35/57 cases (61.4%) and proven in the remainder (22 cases, 38.6%). Eighty percent (33/40) of *Aspergillus* cases with positive culture were identified to the species complex level, and *A.* section *flavi* was the main pathogen (30/33, 90%).

Forty-five cases (67.2%) occurred in male patients and 22 (32.8%) in female. The mean age of patients was 43.16 $\pm$ 13.8 years, ranging from 17 to 72 years. No significant correlation was found between the type of IFI and age or gender.

The most common type of malignancy was AML, with most patients undergoing induction chemotherapy and experiencing a mean duration of neutropenia of 11 days. However, the type of IFI did not significantly correlate with the malignancy characteristics of patients.

Lung imaging revealed fungal infection-associated lesions in 52/67 cases (77.6%), primarily with multiple nodules (64.2%). Sinus imaging also demonstrated fungal infection lesions in 46 cases (68.6%), with mostly showing multiple mucosal thickening. The predominant drug treatments were amphotericin B and voriconazole. Surgical interventions, specifically debridement of necrotic lesions, were performed in 15 cases (22.4%), with 10 performed for aspergillosis and five for mucormycosis management. However, there was no significant association between IFI and lung or sinus involvement.

The overall fatality rate of IFI's was 3.5% (42/1190), and the IFI-attributable mortality rate (AMR) was 62.6% (42/67). The AMR was highest for cases with mucormycosis (71.4%) and it was 61.4% for aspergillosis. Notably, the type of fungus and malignancy did not exhibit a significant relationship with patient outcomes. Demographic data and patient characteristics are summarized in Table 1.

The most common underlying condition identified were central venous catheter (CVC) use, mucositis and antibiotic use. Two patients had no underlying condition other than HM, four had only one risk factor, one patient had 2 risk factors, and 60 patients had three to six risk factors (Table 2).

Table 1: Demographic data and patient characteristics

Variable		Aspergillus N (%)	Mucormycosis N (%)	Other N (%)
Gender	Man	39 (68.4%)	3 (42.9%)	3(100%)
	Female	18 (31.6%)	4(57.1%)	0
Age	<21	3 (5.3%)	0	1(33.3%)
	>21	54 (94.7%)	7 (100%)	2 (66.6%)
	Mean	42.6	51	35
	SD	14.04	7.2	16.7
Malignancy	AML	39 (64.8%)	5 (71.4%)	3(100%)
	ALL	9 (15.8%)	1 (14.3%)	0
	CLL	3 (5.3%)	0	0
	Others	6 (10.5%)	1 (14.3%)	0
Treatment stage	No chemotherapy	4 (7%)	3 (42.9%)	1 (33.3%)
	Induction	34 (59.6%)	3 (42.9%)	1 (33.3%)
	Consolidation	11 (19.3%)	1 (14.3%)	1 (33.3%)
	Salvage	7 (12.3%)	0	0
	Maintenance	1 (1.8%)	0	0
Duration of	Does not have neutropenia	4 (7.1%)	4 (57.1%)	1(33.3%)
Less than 10		29 (50.9%)	1 (14.3%)	2(66.7%)
(days)	>10	24 (40%)	2 (28.6%)	0
Lung imaging	Normal	9(15.8%)	4 (57.1%)	2 (66.7%)
	Nodule	41 (70.2%)	2 (28.6%)	1 (33.3%)
	Consolidation	5 (8.8%)	1 (14.3%)	0
	Ground glass	3 (5.3%)	0	0
Sinus imaging	Normal	19 (33.3%)	1(14.3%)	1(33.3%)
	Single mucosal thickening	7 (12.3%)	3 (42.9%)	1(33.3%)
	Multiple mucosal thickening	31 (54.4%)	3 (42.9%)	1(33.3%)
Simultaneous	No	28 (49.1%)	4(57.1%)	2(66.7%)
lung and sinus involvement	Yes	29 (50.9%)	3(42.9%)	1(33.3%)
Galactomannan	Positive in serum	19 (33.4%)	-	-
	Positive in BAL	2 (3%)	-	-
Type of primary	Caspofungin	4 (7%)	1(14.3%)	1(33.3%)
Medication	Amphotericin deoxycolate	16(28.1%)	2(28.6%)	0
	Amphotericin Liposomal	12 (21.1%)	3(42.9%)	2(66.7%)
	Voriconazole	25 (43.9%)	1(14.3%)	0
Type of	Did not change	25 (43.9%)	4(57.1%)	1(33.3%)
treatment	Caspofungin	2 (3.5%)	0	0
changed	Amphotericin deoxycolate	1(1.8%)	1(14.3%)	0
	Amphotericin Liposomal	3 (5.3%)	1(14.3%)	0
	posaconazole	0	1(14.3%)	0
	Voriconazole	26 (45.6%)	0	2(66.7%)
Surgical	No	47(82.5%)	2(28.6%)	3(100%)
Treatment	Yes	10 (17.5%)	5(71.4%)	0
Outcome	Death	35(61.4%)	5(71.4%)	2(66.7%)
	Recovery	22(38.6%)	2(28.6%)	1(33.3%)

Table 2: Distribution of risk factors for fungal infections in patients with blood malignancy and invasive fungal infections admitted to the blood ward of Shariati Hospital

Risk factors	N	%
Central venous catheter	57	85.1
Mucositis	56	83.6
Taking antibiotics	41	61.2
Previous antifungal prophylaxis	60	89.6
Recent surgery	6	9
Environmental factors (construction around the house)	5	7.5
History of fungal infection	4	6
COPD	3	4.5
DM	2	3
IDU	1	1.5
Previous CMV infection	0	0

DISCUSSION

In recent years, numerous studies have focused on identifying the incidence, risk or prognostic factors for IFI particularly in COVID-19 and transplanted populations. However, the real incidence of these infections in patients with HMs before transplantation has been less appreciated. Revealing the institutional epidemiology of IFIs (incidence rate and predominant etiology) in hematology settings is needed before for implementing antifungal prophylaxis [15].

This study aimed to assess the rate of IFIs, identify the associated risk factors, and explore their consequences in hospitalized patients with HMs over a six-month period. The reported incidence of proven/probable IFI in the different subsets of patients varied from 0.5% among patients with multiple myeloma to 12% in those with AML in series that included both adults and children[12,15]. A similar incidence of (6%) IFIs was documented in our study. Our data corroborate that molds are responsible for the majority of IFI's, with aspergillosis being observed as the most frequent complication in patients with HMs. Notably, similar findings were reported in studies conducted by Kurosawa et al. and Pagano et al. in Japan and Italy, emphasizing aspergillosis as the most common IFIs in patients with malignancies[12,15]. However, unlike these previous studies which reports *A. fumigatus* as the most frequently isolated species[12,15], we demonstrated that *A. flavus* was the most prevailing agent causing aspergillosis in Iran.

Several reports have assessed the incidence of candidemia, particularly in critical care settings. Conversely there are far fewer studies on the rate of candidemia in hematology settings. Our data show that yeast infections are less frequent than mold infections in the setting where an anti-yeast agent (e.g. fluconazole) is widely used as antifungal prophylaxis. However, *Candida spp.* are still the predominant yeast pathogens. In contrast, studies by Lin et al.[16] and León-Borrás et al. [17] demonstrated a higher prevalence of IC, particularly in children with malignancy. Specifically, in the study of León-Borrás et al. in Spain invasive *Candida* infections predominated. In addition, Fracchiolla et al. identified IC and IA as the most common IFI's[18]. In our study, the increased prevalence of aspergillosis could be attributed to the induction phase of

chemotherapy in individuals with AML. Mucormycosis was the second most common IFI, with a reduced risk due to early administration of amphotericin B known for its effectiveness in preventing and treating mucormycosis [19, 20]. Given the aggressiveness and high fatality of mucormycosis, the detection of mucormycosis is presumptively underestimated because in majority of cases death occurred before employing diagnostic procedures, including chest and sinus CT scans. Overall, various studies have recently revealed the apparent increases in the rate of mucormycosis, particularly among those who had received voriconazole for antifungal prophylaxis or treatment. Most cases of mucormycosis identified in the pre-chemotherapy phase indicate an immunodeficiency due to a decrease in leukocytes, especially neutrophils, which predisposes patients to fungal infections and subsequent invasion of the arteries, especially the sinuses. An interesting finding of this study was the observation of two cases of *Fusarium* infection, a relatively rare fungus. In a 10-year study from 2000 in Boston Hospital, only 26 cases of fusariosis were observed [21]. In our population the incidence of both mucormycosis and fusariosis remained low.

Despite the majority of patients having CVC, a known risk factor for candidiasis, candidiasis was observed in only one case. Possible explanations include antifungal prophylaxis, such as fluconazole, prescribed to most hospitalized patients with HM in our institution, reducing the risk of IC [22, 23]. It should be noted that we did not include cases with *Candida* colonization in our assay. Moreover, the method of detection of *Candida* infection in our study was blood culture which has a low positivity rate, so the detection rate of this fungus is probably underestimated. Serological tests which have higher sensitivity than culture based methods such as β-d-Glucan and *Candida* Mannan were not used in our study.

The gender distribution showed no relationship with the type of IFI, and age did not significantly correlate with the fungal infection type. In the study of Fracchiolla et al., the mean age of patients was higher, and there was no significant relationship with the type of fungus[18]. AML was the most common malignancy, consistent with findings by Sheikh Baha'i et al. and Mishra et al. [13] who showed that AML was the most frequent risk factor for IFIs[24]. Another study in Japan also reported AML as the most common type of malignancy complicated by IFIs [12]. Recently, the list of those patients with manifold risk for IFI development has been elongated as several studies reported that purine analogs usage, use of monoclonal antibodies, rituximab or alemtuzumab which prolongs immunosuppression extend the risk of IFI to other patients (e.g. those with CLL) even in the absence of neutropenia or steroid therapy[15]. Moreover, imaging results revealed multiple nodules associated with fungal infections in the lungs, and mucosal thickening in the sinuses. Roughly, half of the cases showed concomitant lung and sinus involvement. In the study of Korula et al., lung involvement was presented in most cases, but sinus involvement was reported in only one-tenth of cases, and only in 2 out of 76 cases, simultaneous lung-sinus involvement occurred [25].

Amphotericin B and voriconazole were the predominant antifungal treatments, with debridement of necrotic lesions performed in one-fifth of cases, mostly related to aspergillosis and mucormycosis. In the study of Fracchiolla et al., the antifungal most often used was amphotericin B[18]. Mortality rates were nearly identical across different fungal types, and no significant association was found between the type of fungus and patient outcomes. Similarly, the type of malignancy did not significantly impact patient outcomes, with death occurring in over half of AML cases. In the study of Kurosawa et al., mortality was not associated with the type of fungal infection [12]. In another study in Taiwan, the highest mortality rate was observed in patients with aspergillosis [16].

Despite the known association between previous cytomegalovirus infection and increased risk of IFIs in individuals with compromised immune systems[26] and HMs[27, 28], none of the subjects in our study had a history of this infection. The study's limitations include potential inaccuracies in information recording, incomplete or distorted data
in some files, a relatively small sample size, and limited access to some patients residing in remote cities.

CONCLUSION

This study revealed that widespread use of anti-yeast prophylaxis has led to significant reduction in candidiasis. However, the predominant fungal infection among patients hospitalized in hematology wards was aspergillosis. AML stands as the most common malignancy for IFIs, often associated with lung and sinus involvement. Despite the high rate of mortality, the study found no significant correlation between the type of IFI and mortality. To gain a more comprehensive understanding, multicenter survey on the prevalence of invasive fungal infections and patterns of antifungal drug resistance across different medical centers is recommended. Additionally, longitudinal studies conducted at longer intervals and the use of specific blood culture methods for *Candida* diagnosis would enhance the depth of insights in subsequent research.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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