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Challenges Faced among Immunocompromised Patients of Hematological Cancers with Invasive Fungal Infection

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Abstract

Background and Objective: Many acute hematological malignancies, including ALL and AML, have the Invasive Fungal Infection[IFI] as a side effect. The IFI raises hospital stays, treatment expenses, and the morbidity and mortality rate of primary diseases. Therefore, the aim of the current study was to determine the challenges faced by acute leukemia cases with Invasive fungal infection among hospitalized patients using clinical and laboratory records.

Patients and Methods: A cross-sectional observational hospital-based prospective study was conducted in our hospital for 6 months. The study included 50 patients with acute hematological malignancies who were admitted to the hospital. The data was entered into an Excel spreadsheet and analyzed using SPSS 29.0. The p-values were obtained using the Chi-square test when applicable.

Results: Twenty-Two Invasive Fungal Infections [IFI] cases were reported among the 50 patients of our study. This correlate with 42% of IFI prevalence. Six [27.27%] of the overall IFI instances were patients with proven IFI, fourteen [63.3%] had probable IFI, and two [9.09%] had possible IFI. There were differences in IFI by sex and age. Patients with Acute Myeloid Leukemia [AML] had a greater prevalence of IFI [47.86 %] than those with Acute Lymphoblastic Leukemia [ALL] [37.03%].

Conclusion: It is evident from the current study that IFI affected AML patients more than it did ALL patients. Invasive non-Albicans candidiasis exacerbated both types, but the AML group experienced more cases. The lungs of both groups were affected followed by bloodstream.

Keywords: Hematological Malignancies; Invasive Fungal Infection; Acute Myeloid Leukemia; Acute Lymphoblastic Leukemia; Candidiasis.

INTRODUCTION

The term "invasive fungal infections" [IFIs] refers to systemic illnesses brought on by the growth of moulds or yeasts in deep tissues. Unlike superficial fungal infections, IFIs are deadly illnesses with a high mortality and morbidity rates [1]. The most prevalent invasive infections that have been identified are caused by species of Aspergillus, Pneumocystis, Cryptococcus, Candida, and others. Furthermore, endemic fungal species such as *Blastomyces, Histoplasma, Paracoccidioides, and Coccidioides* have also been linked to serious systemic infections in people with weakened immune systems [2]. The IFI are frequent side effects of acute hematological malignancies, such as ALL and AML. IFI causes an increase in primary disease morbidity and mortality as well as treatment costs and hospital stays [3].

At various stages of these illnesses, it is impossible to prevent the emergence of weakened states that predispose people to fungal infections. Therefore, prophylactic antifungal treatment is required to stop fungal invasion. To choose the appropriate medication for this reason, one must be aware of the types of invasive fungi. AML patients may develop defective neutrophils, which are essential for resistance to Candida infection, leaving them vulnerable to these opportunistic infections [4].

Another crucial element in containing the aforementioned infection is lymphocyte-mediated cell-mediated immunity. Conversely, Aspergillosis is caused by a decrease in alveolar macrophages, which stops conidia from germinating into tissue-invasive hyphae [5]. Patients are at risk for opportunistic mycoses because antitumor medications cause a neutropenic and lymphocytopenic condition [6].

When the absolute neutrophil count is less than 500 cells/mm3, it is referred to as severe neutropenia [7]. During this phase, opportunistic fungal infections typically manifest. Fungal infections usually begin with febrile neutropenia, which involves severe neutropenia and oral temperature >38.5°C or two consecutive readings of >38°C for two hours [8].

These infections are more likely to occur in critically ill patients receiving broad spectrum antibiotics, those receiving total parenteral nutrition, those suffering from sepsis, renal insufficiency, prolonged hospitalization in the intensive care unit [ICU], and those with cancer that is not yet in remission [9].

A longer stay in the intensive care unit increases the patient's vulnerability to these infections [10]. The mycological profile of infections has changed significantly as a result of the growing use of antifungal prophylaxis [11]. Compared to AML, there are currently few data on IFI in the paediatric population with ALL, according to reports [12].

In patients with unstable clinical conditions or a propensity for bleeding [due to thrombocytopenia from induction chemotherapy], inadequate diagnostic procedures might delay treatment and perhaps compromise the patient's survival [13]. Hence the current study's objective was to use clinical and laboratory records to identify challenges faced by acute leukemia cases with Invasive fungal infection among hospitalized patients.

PATIENTS AND METHODS

A cross-sectional observational hospital-based prospective study was conducted in our hospital from 1.06.2024 to 31.12.2024. The study was conducted after obtaining permission from Institutional Ethics Committee [IEC]. Patients with acute hematological malignancies who were hospitalized were included in the study. Chronic cases of lymphoid and myeloid leukaemia, acute promyelocytic leukaemia and cases of hematological diseases other than malignancy was excluded.

Sample size calculation: A total of 50 patients were studied. Sample size n0=z2pq/e2 [p is the prevalence and q is 1-p.] The prevalence of fungal infections is taken to be 11% [rounded-off]. The value for Z was found in statistical table, which contains area under the normal curve. Here Z=1.96 for 95% confidence. The margin of error here is taken to be 5%.

Data collection procedure: After obtaining written informed consent, all the participants were first questioned using a questionnaire designed in advance to identify AML and ALL cases and gather data regarding fungal infections. In the lab, no cell line was employed for any research. Records of involved myeloid or lymphoid cell lines were used to identify the target population, and a questionnaire was used to classify patients into proven, probable, and possible IFI [or no IFI cases]. If broad spectrum antibiotics failed to treat febrile neutropenia for more than four days, an empirical antifungal was administered. Posaconazole was the prophylactic antifungal medication used in our study, and it was administered only to a limited number of patients. Each patient's baseline information, including age, gender, acute leukemia type, chemotherapeutic stage, complete blood count, and medications used, was gathered. Oral temperature >38.5°C or two consecutive readings of >38°C for two hours are considered febrile episodes. If a fever developed within 12 hours of beginning chemotherapy and went away on its own within the following 24 hours, it was deemed to be caused by the treatment. By collecting a sample from the clinically diagnosed site of infection, the fever episode was examined for any potential fungal infection source. A neutrophil count of less than 500 cells/mm^3 is considered neutropenia. The chest was imaged using High Resolution Computed Tomography [HRCT] to look for radiological signs of an invasive fungal infection.

Statistical analysis: SPSS 29.0 was used to analyze the data after it was entered into an Excel spreadsheet. Where appropriate, the Chi-square test was used to obtain the p-values.

RESULTS

Following a thorough examination of the data, 22 IFI cases were found among the 50 patients who were part of the study. This translates to a 44% IFI prevalence. In the IFI affected population, those with probable IFI made up 14 [63.63%], those with proven IFI made up 6 [27.27%], and those with plausible IFI made up 2 [9.09%]. 2 [9.09%] of the patients in the age category of 22–31 years had the highest number of proved IFI, and 4 [18.18%] of the patients in the age group of 22–31 years had the most likely IFI [**Table 1**].

In our study, 12[54.55%] of the 22 study participants were males, and 10[45.45%] were females. Of the 22 IFI instances, 27.72% of the females and 36.36% of the males had proven IFI. 13.63% of males and females had probable IFI. 9.09% Females had possible IFI, but males had a possible IFI of 4.54% [Table 2]. In the recruited sample, two distinct forms of acute haematological malignancies were taken into consideration. 23 of the 50 patients had AML, and 27 had ALL. Compared to 10 out of 27 ALL patients [37.03%], the prevalence of IFI was greater in 11 out of 23 AML patients [47.82%] [p-value=0.05] [Table 3].

IFI developed in 34 [68%] of the individuals who had received induction treatment. One significant risk factor for the development of IFI was determined to be induction chemotherapy [0.02]. A risk factor for IFI was neutropenia [p=0.05], and the incidence of IFI was observed in 9.09% of patients with neutropenia lasting less than 10 days, 40.90% of patients with neutropenia lasting 10–21 days, and 59.09% of patients with neutropenia lasting more than 21 days [Table 4].

The most frequent site of actual fungal involvement, accounting for 12 [54.54%] of the IFIs, was the lung. Pulmonary infections were caused by invasive aspergillosis and non-Albicans candidiasis. With 8 [36.36%] of the IFIs, the bloodstream was the other site of engagement.

Table [1]: Population distribution based on age and invasive fungal infection status

Age group [years]	Proven IFI	Probable IFI	Possible IFI	Total no. of patients N=22
2-11	0	1 [4.54%]	0	1 [4.54%]
12-21	1 [4.54%]	3[13.63%]	1[4.54%]	5 [22.72%]
22-31	2 [9.09%]	4 [18.18%]	0	6 [27.27%]
32-41	1[4.54%]	3 [13.63%]	0	4 [18.18%]
42-51	1[4.54%]	2 [9.09%]	0	3 [13.63%]
52-61	0	1 [4.54%]	1 [4.54%]	2 [9.09%]
Total	6[27.27%]	14[63.63%]	2 [9.09%]	22 [100%]

Chi-square value=14.2; p-value=0.10

Table [2]: Population distribution based on gender and prevalence of invasive fungal infections [IFI].

Gender	Proven IFI	Probable IFI	Possible IFI	Total no. of patients [N=22]
Male	8[36.36%]	3[13.63%]	1[4.54%]	12[54.55%]
Female	5[27.72%]	3[13.63%]	2[9.09%]	10[45.45%]

Chi-square value=1.02; p-value=0.6

Table [3]: Haematological malignancies based on invasive fungal infections [IFI].

Type of malignancy	With IFI	Without IFI	Total
ALL	10	17	27[54%]
AML	11	12	23[46%]
Total	21[42%]	29[58%]	50[100%]

Chi-square value=16.21; p-value=0.05

Table [**4**]: Population distribution based on phase of treatment, level and duration of neutropenia.

Variables	Total no. of patients [n]	No. of patients with IFI[%]
Type of chemotherapy	50	22[44%]
Induction/Reinduction	34	16 [36.73]
Consolidation	12	6 [27.27]
Maintenance	4	0
Total neutrophil count*	**50**	**22[44%]**
≥500/mm³	22	4[18.18]
<500/mm³ [neutropenia]	28	18 [81.81%]
Duration of neutropenia [in days]	**50**	**22[44%]**
≤10	9	2 [9.09%]
>10-<21	29	7 [31.81%]
>21	12	13 [59.09%]

DISCUSSION

According to the results of our study, 42% of patients with acute hematological malignancies had IFI. This finding was consistent with earlier research that found that 11–30% of patients with acute leukemia had an elevated prevalence of IFI [14].

Patients with acute leukemia may have immunosuppression as a result of the illness or its treatment, which increases their chance of developing IFIs. Similar research produced the same results, which is mostly explained by West Bengal's warm and humid climate were IFI prevalence was 28%, with proven IFI at 13%, probable IFI at 21%, and possible IFI at 66% [15].

Those aged 12 to 41 years had a higher prevalence of IFI [18.18%] than those at the extremes of the age range in this study. This was consistent with another study that found people under 40 had a higher risk of IFI. The median age of the patients in the **Lien MY *et al.*** research was 51 [range: 19–76] [16]. In our study, Males were more likely than females to have IFI in the current study, however the difference was not statistically significant [p-value=0.6].

Females were shown to be significantly more likely to develop IFIs in the **Neofytos D *et al.*** study [17]. This result differed with the study by **Hammond SP *et al.*** which found that the prevalence was 8.75% in females and 17.4% in males [14].

Males are significantly more likely to develop IFI, according to **Zhang R *et al.*** [12] and **Lien MY *et al.*** [16] It has long been believed that the risk of IFI in AML is larger than that in ALL.

The frequency of IFI in AML has been demonstrated to be considerably decreased by the recent inclusion of antifungal prophylaxis to induction chemotherapy[18].

Although the current study supports this, it did not find that, in this age of antifungal prophylaxis, the prevalence of IFI was substantially reduced in ALL patients. Long-term [>10 days] neutropenia has been reported to be strongly linked to invasive fungal infections [19].

Of the 22 patients with IFI, 13 [59.09%] experienced neutropenia for more than 21 days, 7 [31.81%] experienced neutropenia for more than 10 to less than 21 days, and 2 [9.09%] experienced neutropenia for less than 10 days. [12,16]. Fungal infections were more common in AML patients [15 out of 24; 62.5%] than in ALL patients [9 out of 24; 37.5%].

This finding was consistent with studies by **Bhatt VR *et al.*** [3], which reported that 12% of patients had AML and 6.5% had ALL, and

Zhang R *et al*. [12], which indicated that 11.8% of patients had AML and 7.1% had ALL.

The most common site of IFI in leukemia patients was the lung [54.54%], followed by bloodstream [36.36%]. According to Bhatt VR et al., the lung was the most prevalent location, accounting for approximately 75% of IFI [1].

Hansen BA *et al*. [19] and **Tang JL *et al*.**[20] have reported similar findings. The limitation of our study is, a bigger randomized control trial is required.

Conclusion: The current study makes it clear that IFI caused more harm to AML patients than to ALL individuals. Both kinds were compounded by invasive non-Albicans candidiasis, while the group with AML had more instances. Both groups' lungs were impacted by Aspergillus species. Antifungal medications are empirically recommended in situations of hematological malignancies in order to prevent fungal infection.

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