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Research Article

Spectrum of Opportunistic Fungal Infections in Cancer/HIV Patients: Emerging Fungal Pathogens from Jabalpur Madhya Pradesh Central India

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Abstract: The frequency of invasive mycoses due to opportunistic fungal pathogens has increased significantly and is becoming increasingly prevalent in the human population, especially in immunocompromised patients. This increase in infections has found to be associated with excessive morbidity and mortality. It is directly related to increasing patient populations at risk for the development of serious fungal infections. A total of 88 cases of patients suffering from various types of cancer, and an HIV positive patient was investigated. Among them, 36 (41 %) cases were found to be positive for the occurrence of fungal infections. Out of 36 cases 20 (55.5 %) patients were male and 16 (44.4 %) were females. Amongst females almost all were suffering from cervix cancer 87 %, followed by breast cancer. Total 54 isolates were obtained, including 29 (54%) isolates of filamentous fungi and 25 (46%) isolates were yeast. *Aspergillus* species 17 (47 %) have been the most frequently isolated fungi followed by yeast *Candida* 12 (33%). In this study apart from Aspergillus, non–aspergillus species belonging to phaeohyphomycetes and hyalohyphomycetes were also isolated. Dematiaceous fungi isolated included *Cladosporium* sp., *Alternaria* sp., *Curvularia* sp.. Hyaline fungi isolated were *Geomyces pannorum*, *Acremonium* sp., *Humicola* sp., *Wallemia sebi*. Amongst *Candida* the non -albicans were 10 (83 %) and albicans were 2 (17 %). Amongst yeasts, *Candida versatilis* were abundant that is 5 (20%) followed by *Debaryomyces hensenii* 3 (15 %) and then *Candida albicans* 2 (8 %). *Cladosporium* sp. and *Alternaria alternata* were the fungi that were isolated with high frequency amongst filamentous fungi after *Aspergillus* sp. that is 3 (10.3 %). Some newly identified isolates were also reported *Candida fennica*, *Sacchaniomyces occidentalis*, *Candida versatilis*, *Humicola* sp., *Candida fusiformata*, *Cryptococcus albidus*, *Cryptococcus macerans*, *Aspergillus versicolor*, *Kluyveromyces maxianus*, *Wallemia sebi* etc.
Keywords: Fungal infections, Neutropenia, Opportunistic fungal infections, Cancer/ HIV patients.

INTRODUCTION

Fungal infections in the immunocompromised cancer patient may threaten the survival and represent a major therapeutic challenge. Major advances in anticancer treatment have contributed to an increased frequency of severe fungal infections in patients with neoplastic diseases. CNS infections are frequently caused by viral, bacterial, or fungal pathogens and are described in their clinical presentation, their diagnostic procedures and the best possible therapeutic and prophylactic management [1]. Fungal infections can emerge as a part of nosocomial infection and their monitoring should be included in the programme of Nosocomial Infection Prevention Committees (CLIN) [2].

Neutropenia remains the most important among the predisposing factors related to the malignancy or its treatment. Granulocytopenia, especially, increases the risk of infection with the two most common fungal species, *Candida* and *Aspergillus* [3]. However, recently newer pathogens such as Pheohyphomycetes, Hyalohyphomycetes, Zygomycetes and other fungi of emerging importance, such as *Torulopsis glabrata*, *Trichosporon beigelii*, *Malassezia* spp, *Saccharomyces* spp, *Hansenula* spp, *Rhodotorula* spp, and *Geotrichum candidum* have appeared as significant causes of infection in this patient population [4]. Apart from an expanding number of different Zygomycetes, previously uncommon hyaline filamentous fungi (such as *Fusarium* species, *Acremonium* species, *Paecilomyces* species, *Pseudallescheria boydii*, and *Scedosporium prolificans)*, dematiaceous filamentous fungi (such as

Bipolaris species, *Cladophialophora bantiana, Dactylaria gallopava, Exophiala* species, and *Alternaria* species) and yeast-like pathogens (such as *Trichosporon* species, *Blastoschizomyces capitatus, Malassezia* species, *Rhodotorula rubra* and others) are increasingly encountered as causing life threatening invasive infections that are often refractory to conventional therapies. On the basis of past and current trends, the spectrum of fungal pathogens will continue to evolve in the settings of an expanding population of immunocompromised hosts, selective antifungal pressures, and shifting conditions in hospitals and the environment. The lethality of opportunistic fungal infection is high despite a growing arsenal of antimycotic drugs, implying the urgent need for supportive immunological therapies to strengthen the current inefficient antimicrobial defenses of the immunocompromised host. Therefore, increasing effort has been directed to investigating the interplay between fungi and the host immunity and thus to find starting points for additional therapeutic approaches [5].

MATERIALS AND METHODS

In the present study, we have investigated the different body fluids as clinical samples (peripheral blood, urine and sputum) of different categories of 88 cancer/ HIV positive patients for fungal infections. The screening of these patients was done from Cancer Hospital of Netaji Subhash Chandra Bose Government Medical College and few other private clinics of Jabalpur (M.P.)

Collection and isolation from Blood:

About 5 ml of blood was collected aseptically by vein puncture from the patients and immediately transferred to a previously sterilized bottle in 1:10 ml of Sabouraud's dextrose broth with heparin as an anticoagulant. The bottle was agitated rapidly, but gently to ensure proper mixing of the blood with anticoagulant. The bottle with the mixture was then incubated for 24h at 28 ± 1° C. After incubation the blood sample was incubated on Sabouraud's dextrose agar slants (SDA), the inoculated slants were incubated at 28° C for 7 days before concluding as negative.

Collection and isolation from Urine

Early morning first urine samples were used for mycological investigations. About 5 ml of midstream urine was collected from the patients in sterilized wide mouth plastic bottles. The samples were then centrifuged at 2000 rpm for 15 minutes. Supernatant was discarded and the sediment of urine was inoculated on SDA slants with 0.05mg/ml chloramphenicol.

Collection and isolation from Sputum

Sputum samples were collected from patients suspected of bronchopulmonary carcinoma. The samples were collected in sterilized wide mouth plastic bottles after the patients had brushed their teeth or washed their mouth with sterile water. Only fresh early morning samples were collected. Sputum samples collected were homogenized with sterile glass beads. Equal amount of phosphate buffer (pH 6.8 - 7.1) and chloramphenicol (0.05 mg/ml) was thoroughly mixed with it. About 0.1 ml of homogenized sputum was inoculated into SDA slants with chloramphenicol (0.05 mg/ml) and incubated for 7 days at 28 ± 1^0C. These slants were observed daily for growth of fungus. During the isolation process control slants were also kept in order to rule out any chances of false result.

Identification of the isolates

Identification of filamentous fungi - The filamentous fungi was identified on the basis micro and macro morphological studies [6, 7]. The identification was further confirmed by Prof. Josep Guarro, Spain. The isolates were regularly sub cultured to maintain their viability.

Identification of yeasts

Yeast isolates were identified by performing morphological and biochemical studies fermentation, assimilation, germ tube formation, chlamydospore formation, cyclohexamide test [6, 7].

RESULTS

In this retrospective study about 88 clinical samples of blood, urine and sputum from immunocompromised patients were screened, and investigated for detection of the presence of any pathogenic fungi. Out of 88 cases studied 36 (41 %) cases were found to be positive for fungal infections. A total of 54 isolates were obtained during the course of study. Out of which 29 (55%) were filamentous fungi and 25 (45 %) were yeasts. Male to female ratio was found to be 1.25, thus males outnumbered female patients in the present study. *Aspergillus* species 17 (47 %) were the most frequently isolated fungi followed by yeast *Candida* 12 (33%). Amongst *Candida* the non *albicans* were 10 (83 %) and *albicans* were 2 (17 %). Amongst yeasts, *Candida versatilis* were abundant that is 5 (20%) followed by *Debaryomyces hensenii* 3 (15 %) and then *Candida albicans* 2 (8 %). After these yeasts *Cladosporium* sp. and *Alternaria alternata* were the fungi that were isolated with high frequency amongst filamentous fungi after *Aspergillus* sp. that is 3 (10.3%) (Table 1). *Torulospora delbrueckii Candida versatilis Acremonium* sp. *Curvularia* sp. *Trichosporon ashaii, Candida kefyr, Rhodotorula, Pichia anomala, Geomyces pannorum and Trichosporon beigelii* each were isolated .Some new emerging pathogens reported from first time *Candida fennica, Sacchaniomyces occidentalis, Candida versatilis, Humicola* sp., *Candida fusiformata, Cryptococcus macerans, Aspergillus versicolor, Kluyveromyces maxianus, Wallemia sebi* etc. Table1. Shows the details of all the cases studied along with the results of direct microscopy and fungal isolates obtained from the respective clinical samples.

Table 1: Shows the details of all the cases studied along with the the results of direct microscopy and fungal isolates obtained from the respective clinical samples

Sl. No.	Sex/ Age	Underlying disease	Neutrophil count in %	Clinical Sample	Result of Direct microscopy	Filamentous fungi/yeast isolated
1	F/46	Cervix Cancer II	10	Peripheral blood	Negative	*Aspergillus fumigatus, Candida fennica*
				Urine	Positive	*Debaryomyces hansenii*
2	F/60	Cervix Cancer II	14	Peripheral blood	Negative	*Aspergillus fumigates, Sacchaniomyces occidentalis*
				Urine	Positive	*Aspergillus terreus* and *Torulospora delbrueckii*
3	F/35	Cervix Cancer III	11	Blood	Positive	*Aspergillus flavus, Cladosporium*
				Urine	Positive	*Candida versatilis*
4	M/75	Prostate Cancer	19	Blood	Negative	*Cryptococcus albidus*
				Urine	Positive	*Aspergillus terreus*
5	M/45	Bronchial Carcinoma	21	Blood	Negative	*Aspergillus flavus, Acremonium* sp.
				Urine	Positive	*Sachaniomyces occidentalis*
6	M/45	Gall Bladder Cancer		Urine	Positive	*Candida versatilis*
7	M/56	Carcinoma Lungs	24	Blood	Negative	*Curvularia* sp.
				Urine	Negative	*Candida versatilis*
8	F/35	Cervix Cancer II	17	Blood	Negative	*Humicola* sp.
				Sputum	Positive	*Trichosporon asahii*
9	F/35	Cervix Cancer II	26	Blood	Positive	*Alternaria alternate*
10	F/40	Cervix Cancer III	16	Blood	Positive	*Alternaria alternate*
11	M/42	Carcinoma Lungs	26	Branchial lavage	Positive	*Candida fusiformata*
13	F/30	Cervix Cancer III	18	Blood	Positive	*Debaromyces hansenii*
				Blood	Negative	*Aspergillus fumigatus*
14	F/40	Cervix Cancer III	23	Urine	Negative	*Candida albicans*
15	F/45	Cervix Cancer III	19	Blood	Positive	*Aspergillus terrus*
					Positive	*Cryptococcus macerans*
16	F/40	Cervix Cancer III	10	Blood	Positive	*Aspergillus versicolor*
17	M/45	Liver Cancer	18	Blood	Positive	*Cladosporium* sp, *Kluyveromyces maxianus*
18	M/41	Rectal Cancer	34	Urine	Positive	*Candida kefyr*
19	M/55	Larynx Cancer	30	Blood	Negative	*Aspergillus flavus*
				Urine	Positive	*Aspergillus flavus*
20	M/49	Thyroid Cancer	21	Urine	Positive	*Rhodotorula*
21	M/49	Liver cancer	22	Blood	Negative	*Asperigillus terrus*
				Urine	Positive	*Asperigillus fumigatus*
22	M/54	Ca.Tongue	35	Urine	Positive	*Candia versatilis*
				Sputum	Positive	*Candida versatilis*
23	M/56	Carcinoma palate	29	Blood	Positive	*Pichia anomala*
24	M/52	Larynx Cancer	34	Blood	Positive	*Candida albicans*
				Urine	Positive	*Fusarium oxysporum*
25	F/29	Breast Cancer	27	Blood	Positive	*Alternaria alternata*
				Urine	Positive	*Candida tropicalis*
26	F/50	Cervix Cancer	31	Blood	Positive	*Debaromyes hansenil*
27	F/30	Cervix Cencer	27	Blood	Positive	*Aspergillus versicolor*
28	F/35	Cervix Cancer	24	Blood	Negative	*Wallemia sebi*
29	M/45	Chronic Myleoid Leukemia	16	Blood	Positive	*Aspergillus fumigatus*

30	M/35	Thyroid Cancer	27	Blood	Positive	*Aspergillus fumigatus, Geomyces pannorum*
31	M/50	Ca.Tongue	22	Urine	Positive	*Candida glabrata*
32	M/55	Pharyngeal Cancer	24	Blood	Positive	*Aspergillus glaucus*
				Urine	Positive	*Fusarium* sp.
33	M/25	HIV, AIDS III Stage	9	Blood	Positive	*Aspergillus terrus, Cladosporium cladosporoides*
34	F/58	Breast Cancer	33	Blood	Positive	*Cladosporium* sp.
35	M/35	Cheek Ca	32	Urine	Positive	*Candida glabrata*
36	M/50	Ca. Pharynx	33	Urine	Positive	*Trichosporon beigelii*

Ca.=Carcinoma, M =Male, F =Female

DISCUSSION

A steady increase in the frequency of invasive fungal infections has been observed in the past few decades, particularly in immunosuppressed patients. Periods of prolonged neutropenia with neutrophil count less than 0.5 x 10(9)/L longer than 7 days, is the most important risk factors for the development of systemic fungal infections [8]. Chamilos *et al*. in year 2006 evaluated autopsy-proven invasive fungal infections (IFI) in patients with hematologic malignancies over three periods. They showed that the prevalence of invasive mold infections increased significantly (p=0.05) in parallel with the emergence of zygomycetes (p=0.03) [9]. In our studies, we have been encountered with several patients suffering from such malignancies.

In recipients of bone marrow transplants, *Candida albicans* and *Aspergillus fumigatus* remain the primary pathogens. In many centers, however, *Candida* species other than *C. albicans* now predominate, and many cases of aspergillosis are due to species other than *A. fumigatus* [10]. At the Mycology Center, 1006 isolates from a wide range of clinical samples were studied during 1999-2001. *Candida albicans* (40.3%) was the most isolated species, although, the *Candida* non albicans species with 54.9% showed the major prevalence. In blood cultures *Candida parapsilosis* (34.9%), *C. albicans* (30.2%) and *C. tropicalis* (25.6%) were recovered most frequently while *C. glabrata* represented only 2.3%. *C. albicans* with 60%-80% was the predominant specie in mucosal surface. Urinary tract infections caused by yeasts were more frequent in hospitalized patients, being *C. albicans* (47.7%), the most commonly isolated, followed by *C. glabrata* (24.8%) and *C. tropicalis* (20.0 %) [11]. In India phaeohyphomycosis has not been adequately studied and reported in contemporary medicine. Singh *et al*. (1992) reported *Sporotrichum pruninosum* and *Cladosporium oxysporum* to be associated with bronchopulmonary disorder in a patient [12]. In the present study we have seen occurrence of phaeoid fungi like *Cladosporium* sp. in patient positive for HIV.

Although *Candida* and *Aspergillus* species remain the most common fungal pathogens, multiple unusual fungal pathogens are being increasingly recognized as a cause of infection in these patients. Many of these rare fungal infections have a characteristic clinical disease spectrum. Early diagnosis and prompt treatment of these infections is the key to a successful outcome. Few works were documented to study the epidemiology, pathogenesis, clinical features, and approach to the management of infections caused by *Fusarium, Zygomycetes, Scedosporium, Trichosporon, Malassezia, Alternaria, Paecilomyces, and Penicillium.* [13-18]. In the present study also we obtained several non *Candida albicans* species like *Candida versatilis, Candida fennica, Candida fusiformata, Candida kefyr, Candida glabrata, Candida tropicalis* and non *Aspergillus fumigatus* species like *Aspergillus flavus, Aspergillus terreus, Aspergillus versicolor.*

Fungi such as *Fusarium* species, *Trichosporon* species, *Curvularia* species, and *Alternaria* species previously were thought to represent contamination or harmless colonization when isolated from immunocompromised patients. More recently, the pathogenic role of these and other fungi has been clearly established. Three diverse groups of fungi are responsible for these emerging infections: the agents of phaeohyphomycosis and hyalohyphomycosis and certain yeasts [19]. Recent research showing the direct involvment of moulds in causing substantial infections in the immunocompromised hosts. Evidences also suggests that infections caused by rare and emerging pathogens are increasing even with the administration of broad spectrum antifungal prophalyxis and improved survival times placing immunocompromised patients at risk for longer [20, 21]. In the our study we have obtained *Fusarium* sp., *Cladosporium* sp., *Alternaria alternata, Acremonium* sp., and few fungi that were first time reported to be isolated from blood such as *Humicola* sp., *Wallemia sebi and Geomyces pannorum.*

Apart from *Candida* non *Candida* species of yeasts were also isolated. These included *Cryptococcus albidus, Cryptococcus macerans, Debaryomyces hansenii ,Rhodotorula* sp., *Sacchaniomyces occidentalis, Pichia anomala ,Trichosporon ashaii* and *Trichosporon beigelii.* Less-common pathogenic yeasts (*Malassezia, Trichosporon, Rhodotorula, Debaryomyces* and *Pichia*) have recently been reported, with increased frequency, as causes of nosocomial

infections with high mortality [22]. The likelihood of developing a fungal infection increases with the severity and duration of neutropenia, which, in the case of cancer or chemotherapy for the treatment of hematological malignancies, can range from a few days to several weeks [21, 23]. The diagnosis of fungal infection in immunocompromised cancer patients is difficult for the clinician while the risk of fungal infection is high in patients with prolonged fever and neutropenia who do not receive antifungal therapy [24]. Such type of infections in immunocompromised patients as well as solid organ transplant (SOT) cases have been studied and viewed by several investigators. Their findings suggests that advanced diagnostic methods including advanced imaging methods have evolved to pin point on the presence of fungal etiological agents in several type of clinical samples including brain [25, 26]. Another finding was isolation of multiple organisms from the same patient though from different sites. However in few cases same species were isolated from different sites. Similar findings were also reported by Ellen *et al*. where they reported multiple organisms from single site [27, 28]. The patients investigated in our study were suffering from some or the other debilitating disease which has lead to reduced immunity and had made them a target of the opportunistic fungal pathogens. These pathogens find a way to enter into the human body and slowly transform to pathogenic forms. Few of them like *Candida* sp. could be normal commensal of the body and when get a chance can become pathogenic.

CONCLUSION

The present work is an effort to highlight the chances of rare emerging pathogens to transform into pathogenic ones and bring the attention of both the clinicians and microbiologists to take the opportunistic fungal infection at par to other secondary infections.

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