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Survey of Invasive Fungi from Patients with Malignancies

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A B S T R A C T

The aim of this study was to evaluate the incidence of invasive fungal infections (IFIs) in adult and pediatric patients with malignancies, in Assuit governorate, Egypt. This was done by revealing of fungal infection in Blood samples collected from 22 patients with malignancies (from 2-89 years old), from South Egypt Cancer Institute in Upper Egypt, Assiut. Thirty four species invasive fungi belonging to 11 genera were isolated from blood samples on Sabouraoud's Dextrose Agar (10 genera and 26 species) and Rose Bengal Chloramphenicol Agar (9 genera and 22 species) media. *Aspergillus* (7 species), *Penicillium* (11 species), Yeasts (3 species) and *Cladosporium* (2 species) contributed the broadest spectra of species in all samples tested on two types of media used. Other species were represented by 11 species belonging to 7 genera. A variety of type of filamentous fungi were obtained from hematologic malignancies patients. Further studies are needed to confirm this microbiological trend patients with hematologic malignancies, the results of which might be helpful to improve the management of these patients such as especial care from Clinical, food, drinking and air.

Introduction

Invasive fungal infections (IFIs), in particular invasive mould infections (IMIs), were an important cause of mortality amongst patients with haematological malignancies (Galimberti *et al.*, 1998 and Morgan *et al.*, 2005). Invasive fungal disease (IFD) has high mortality rate, especially in the growing population of immunocompromised patients and mortality in patients with hematological diseases (Kontoyiannis *et al.*, 2010; Pagano *et al.*, 2010; Ozsevik *et al.*, 2015; Ruangritchankul *et al.*, 2015). The epidemiology of invasive fungal infections (IFIs) in onco-hematological patients has changed substantially in recent years and its incidence varies considerably among different nations (Chamilos *et al.*, 2006;

Pagano *et al.*, 2007; Nosari *et al.*, 2001). A special vulnerability to these infections is introduced by risk factors related to the underlying disease e.g., neutropenia especially for acute myeloid leukemia patients, invasive medical devices (Lass-Flörl, 2009; Viscoli *et al.*, 2005).

These events have led to the recently reported improvement in the prognosis of patients with this life threatening infection (Pagano *et al.*, 2006; Neofytos *et al.*, 2009; Nicolle *et al.*, 2011). Invasive fungal disease (IFD), predominantly aspergillosis, is associated with significant morbidity and mortality in immunocompromised patients, especially those with haematological malignancies and recipients of allogeneic haematopoietic stem cell transplantation (Akan *et al.*, 2013). Maschmeyer *et al.*, (2007) observed that Invasive aspergillosis was a life-threatening infection in patients with hematological malignancies undergoing intensive cytotoxic chemotherapy. Invasive fungal infection (IFI), caused by both yeasts and moulds, is a persistent problem, with high morbidity and mortality rates among patients on chemotherapy for hematology diseases, and hematopoietic stem cell transplant recipients (Vallejo-Llamas and Ruiz-Camps, 2012).This study aims to isolate and define invasive fungal species from clinical blood specimens of patients with malignancies.

Patients and Methods

Collection of Clinical Blood Specimens

Twenty two clinical specimens of blood culture were collected from malignancy patients (age ranged from 2-89 years old) from South Egypt Cancer Institute in Upper Egypt, Assiut. Blood samples were collected under complete aseptic conditions. A 5mL of blood was introduced in to avacutainer containing 50 mL nutrient broth, blood culture medium was then mixed by vigorously inverting 4-5 time. The bottle was incubated at 37°C for 7-10 days or more if a slowly growing organism s are suspected. The culture examined daily for evidence of growth which is detected daily by the presence of hemolysis or turbidity if growth was evident.

Isolation Media

The plating technique was employed for determination of fungi of blood samples. About 1 mL blood from each sample was scattered on the surface of each of two isolation media (Sabouraoud's Dextrose Chloramphenicol Agar and Rose Bengal Chloramphenicol Agar media). Six plates were used for each blood sample (three plate for each type of media) plates were incubated at 28°C for1-2 weeks and developing fungi were counted, isolated, and identified and the counts was calculated per 1mL urine in each sample. Repeated sub-culturing on Sabouraoud's Dextrose Chloramphenicol Agar was essential to obtain pure cultures. Sporulation was induced by exposing the cultures to ultraviolet light. Isolates were characterized according to morphological features, cultural characteristics such as pigmentation of the mycelium and direction of growth of the hypha, whether aerial or lateral, microscopic observation of structures involved in asexual reproduction, e.g. conidia or spores, and in sexual reproduction, and the presence of fruiting bodies. Light photomicrographs were taken mostly from slide cultures. Slide cultures were performed by removing a small cylinder of the agar medium by a cork borer, and inserting it on the surface of the same agar inside a Petri dish. The top of the cylinder was inoculated with the fungus and covered with a sterilized cover slip. After

few days, the fungus growing on the cover slip is gently stained with cotton blue and mounted in lactophenol. Identification was accomplished using appropriate taxonomic techniques, such as those of (AUMC, 2014; Kauffman *et al.,* 2006; Moubasher 1993; Pitt and Hocking 2009). While the yeast cultures were identified primary in our laboratory and sent to molecular (Sol Gene, Korea) for identification (Scherer and Stevens 1987; White *et al.,* 1990; Buitkamp *et al.,* 1991).

Results and Discussion

Thirty four species invasive fungi belonging to 11 genera were isolated from 22 blood samples on Sabouraoud's Dextrose Agar (10 genera and 26 species) and Rose Bengal Chloramphenicol Agar (9 genera and 22 species) media (Table 1, 2).

Invasive Fungal Infections on Sabouraoud's Dextrose Chloramphenicol Agar Medium

Twenty six species invasive fungi belonging to 10 genera were collected from 22 blood samples on Sabouraoud's Dextrose Chloramphenicol Agar at 28 ±2 °C for 1-2 weeks (Table 1).

The total count of fungi in blood samples widely ranged between (3-50) colonies/mL, the highest count was estimated in sample No 15, where patient suffered from Acute lymphoblastic leukemia.

The presented data in (Table 1) showed that the counts of *Aspergillus* ranged between 1-26 colonies/mL blood the highest count was estimated in sample No(9),and was recovered in high frequency occurrence 68.2 % of the sample constituting 47.15 % of total fungi. Where patient suffered from Acute lymphoblastic leukemia. It was represented by 6 species of which *A. flavus var. columnaris, A. niger and A. terreus var. terreus* were isolated in low frequency. They emerged in 27.3, 27.3 and 18.2 % of samples matching 41.9, 30.6, and 16.1 % of total *Aspergillus* and 19.8, 14.4 and 7.6 % of total fungi, respectively (Table 1). Where patients suffered from Acute lymphoblastic leukemia and Non-Hodgkin's lymphoma *A. flavus var. flavus, A. fumigatus*, and *A. gigantes* counts ranged between (9, 1-2, and 2) colonies/mL blood and the highest counts were estimated in samples No. 10, 19 and 14respectively. And was isolated in low frequency. They emerged in 4.5, 9.1 and 4.5 % of samples matching 7.25, 2.4, and 1.6 % of total *Aspergillus* and 3.4, 1.4 and 0.76 % of total fungi, respectively. Where patients suffered from Acute lymphoblastic leukemia, Hodgkin's lymphoma and Testicular seminoma.

Cladosporium was ranked second in the number of cases of isolation and moderate frequency of occurrence. It was recovered from 31.8 % of the samples constituting 4.7 % of total fungi. It was represented by 2 species and these were *C. cladosporioides* and *C. oxysporum* were isolated in moderate or rare frequency of occurrence. They were recovered in 31.8 and 4.5 % of the samples and 4.2 and 0.38 % of total fungi, respectively. Where patients suffered from stomach Cancer, Hodgkin's lymphoma and Non-Hodgkin's lymphoma.

Also the data in (Table 1) showed that *Penicillium* occupied the third place in the number of cases of isolation and moderate frequency of occurrence. *Penicillium* was recovered from 31.8 % of the samples comprising 8.4 % of total fungi. It was represented by 8 species; *P. brevicompactum, P. chrysogenum, P. crustosum, P. duclauxii, P. glabrum,P. griseofulvum, P. islandicumand P. verrucosum* were isolated in rare frequency

occurrence. They were recovered in 9.1, 9.1, 4.5, 4.5, 4.5, 9.1, 9.1 and 4.5 % of the samples matching 0.8, 3.0, 0.8, 0.8, 1.1, 0.8, 0.8 and 0.4 % of total fungi, respectively. Where patients suffered from stomach Cancer, Hodgkin's lymphoma and Non-Hodgkin's lymphoma. (Table 1).

While the data in (Table 1) showed that *Acrophialophora fusispora, Alternaria (A. alternate and A. chlamydospora), Cochliobolus lunatus, Fusarium (F. chlamydosporum and F.dimerum), Mucor racemosus, Scopulariopsis* and Yeasts (*Debaryomyces hansenii* and *Zygowilliopsis californica*), were recovered in rare frequency of occurrence, respectively. Where patients suffered from stomach Cancer, Hodgkin's lymphoma and Non-Hodgkin's lymphoma.

Invasive Fungal Infections on Rose Bengal Chloramphenicol Agar Medium

Twenty two species invasive fungi belonging to 9 genera were isolated from 22 blood samples on Rose Bengal Chloramphenicol Agar at 28 ±2 °C for 1-2 weeks (Table 2).

The total count of fungi in blood samples widely ranged between (2-53) colonies/mL, the highest count was estimated in sample No 17, where patient suffered from Acute lymphoblastic leukemia.

The presented data in (Table 2) showed that the counts of *Aspergillus* ranged between 1-21 colonies/mL bloods the highest count was estimated in sample No(12), and was recovered in 63.6 % of the sample constituting 44.2 % of total fungi. It was represented by 5 species of which *A. flavus var. columnaris* was isolated in high frequency occurrence. It was recovered in 50.0 % of the samples matching 49.0 % of total *Aspergillus* and 21.7 % of total fungi, respectively. *A. flavus var. flavus* and *A. niger* were isolated in moderate frequency occurrence. They were recovered in 22.7, and 31.8 % of the samples matching 12.7 and 26.4 % of total *Aspergillus* and 5.6 and 11.7 % of total fungi, respectively. *A. ochraceus* and *A. terreus var. terreus* were isolated in rare frequency occurrence. They were recovered in 9.1 % of the samples matching 3.9 and 7.8 % of total *Aspergillus* and 1.7 and 3.5 % of total fungi, respectively. Where patients suffered from Acute lymphoblastic leukemia, Hodgkin's lymphoma and Testicular seminoma.

The presented data in (Table 2) showed that *Cladosporium* was ranked second in the number of cases of isolation and moderate frequency of occurrence. It was recovered from 36.4 % of the samples constituting 15.2 % of total fungi. It was represented by 2 species and these were *C. cladosporioides* and *C. oxysporum* were isolated in moderate or rare frequency of occurrence. They were recovered in 31.8 and 4.6 % of the samples and (13.4 and 1.7) % of total fungi, respectively.

Also the data in (Table 2) showed that *Penicillium* occupied the third place in the number of cases of isolation and moderate frequency of occurrence. *Penicillium* was recovered from 36.4 % of the samples comprising 16.5 % of total fungi. It was represented by 6 species; *P. chrysogenum* was isolated in low frequency occurrence. It was recovered in 22.7 % of the samples matching 6.5 % of total fungi, respectively. While *P. aurantiogriseum, P. citrinum, P. crustosum, P. griseofulvum* and *P. pinophilum* were isolated in rare frequency, they were recovered in 4.6, 22.7, 9.1, 9.1 4.6 and 4.6 % of the samples, matching in 0.4, 4.8, 1.7, 2.2 and 0.9 % of total fungi, respectively. Where patients suffered from stomach Cancer, Hodgkin's lymphoma and Non-Hodgkin's lymphoma (Table 2).

The data in (Table 2) showed that *Acrophialophora fusispora, Alternaria (A. alternate and A. chlamydospora), Fusarium oxysporum, Scopulariopsis (S. candida and S. brevicaulis) Ulocladium atrum,* and Yeast (*Candida glabrata* and *Zygowilliopsis californica*), and were recovered in rare frequency of occurrence, respectively.

Molecular Characterization of Three Different Yeasts Species

For this purpose, partially ITS1 18S rRNA gene of these isolates was amplified and sequenced 560bp for *Candida glabrata* with gen Bank accession No. KM588310, 610bp for *Debaryomyces hansenii* with genBank accession No. KM521205, and 544bp for *Zygowillipopsis californica* with genBank accession No. KM593661.

The Most Common Pathogenic Fungi Isolated from Blood Samples

Fungal distribution was varied according to the type of cancer, where patients suffered from cancer bladder disease, ALL disease, NHL cancer disease, HL disease, stomach cancer disease, nuroblastoma disease, testicular seminoma disease, tumor vertebral columnar disease and Brian tumor disease, the most common pathogenic fungi was *A.niger, A. flavus var. columnaris, A. flavus var. columnaris, P. chrysogenum, A. flavus var. columnaris, A. terreus var. terreus,*(*A. fumigatus, A.niger* and *P. crustosum*), *Candida glabrata and A.niger* respectively.

Where organism appeared in 100, 21, 25.8, 40, 40, 82, 22, 69 and 33.3 % respectively from total colonies and this is showed in (Table.3). The results indicate that immunocompromised patient is a suitable habitat for the growth and sporulation of different groups of fungi, both saprophytic and pathogenic. A variety of types of filamentous fungi and identified yeasts were obtained from blood samples of malignancies patients. It is clear that the treatment of patients with chemotherapy induced invasive fungal infection and has an effect on the numbers and diversity of fungal colonies existing from fluids of malignancies patients, this agreed with (Kiwan and Anaissie, 1999), who observed that fungal infections were much more common in patients with compromised immune system.

Aspergillus (7 species), *Penicillium* (11 species), *Yeasts* (3 species) and *Cladosporium* (2 species) contributed the broadest spectra of species in all samples tested on two types of media used. Other species were represented by 19 species belonging to 14 genera. The fungal population on Sabouraoud's Dextrose Chloramphenicol Agar medium from malignancies patients was more than that have been isolated on Rose Bengal Chloramphenicol Agar medium. These results may be due to the differences in meteorological data. Daily mean temperature, humidity, maximum wind speed, spore counts and rainfall near the university hospital (Fourneret-Vivier *et al.*, 2006). Some species were isolated only on Sabouraoud's Dextrose Chloramphenicol Agar (2 species from *Aspergillus* (*A.fumigatus* and *A.giganteus*), *Cochliobolus lunatus, Fusarium dimerum, Mucor racemosus,* 5 species from *Penicillium* (*P. brevicompactum, P.duclauxii, P.glabrum and P.islandicum and P.verrucosum*) and *Debaryomyces hansenii, Aspergillus ochraceus, Fusarium oxysporum,* 3 species from *Penicillium* (*P. aurantiogriseum, P. citrinum* and *P.pinophilum*), *Scopulariopsis brevicaulis* and *Candida glabrata* were encountered only from urine samples on Rose Bengal Chloramphenicol Agar medium.

Table.1 Fungi isolated from Blood samples on Sabouraoud's Dextrose Chloramphenicol Agar medium

Isolation Media	**Sabouraoud's Dextrose chloramphenicol agar**			
Genera & species	**TC**	**F 1%**	**NCI &OR**	**F2 %**
Acrophialophora fusispora (S.B. Saksena) Samson 1970	1	0.4	1R	4.6
Alternaria	5	1.90	3R	13.6
A. alternata(Fr.) Keissl. 1912	2	0.76	2R	9.1
A. chlamydospora Mouch. 1973	3	1.14	2R	9.1
Aspergillus	124	47.15	15H	68.2
A. flavus var. columnaris Raper& Fennell 1988	52	19.77	6L	27.3
A. flavus var. flavus Link 1809	9	3.42	1R	4.6
A. fumigatus Fresen. 1863	3	1.14	2R	9.1
A. giganteus (Mattlet) Basgal 1931	2	0.76	1R	4.6
A. niger sensu auct. pro parte, pre 2007	38	14.45	6L	27.3
A. terreus var. terreus Thom 1918	20	7.60	4L	18.2
Cladosporium	12	4.6	7M	31.8
C. cladosporioides (Fresen.) G.A de. Vries 1952	11	4.18	7M	31.8
C. oxysporum Berk. & M.A. Curtis 1868	1	0.38	1R	4.6
Cochliobolus lunatus R.R. Nelson & F.A. Haasis 1964	2	0.76	1R	4.6
Fusarium	4	1.52	2R	9.1
F. chlamydosporum Wollenw. &Reinking 1925	1	0.38	1R	4.6
F. dimerum Penz. 1882	3	1.14	1R	4.6
Mucor racemosus Fresen. 1850	3	1.14	2R	9.1
Penicillium	22	8.4	7M	31.8
P. brevicompactum Dierckx 1901	2	0.8	2R	9.1
P. chrysogenum Thom 1910	8	3.0	2R	9.1
P. crustosum Thom 1930	2	0.8	1R	4.6
P. duclauxii Delacr. 1891	2	0.8	1R	4.6
P. glabrum (Wehmer) Westling 1911	3	1.1	1R	4.6
P. griseofulvum Dierckx 1901	2	0.8	2R	9.1
P. islandicum Sopp 1912	2	0.8	2R	9.1
P. verrucosum Dierckx 1901	1	0.4	1R	4.6
Scopulariopsis candida Vuill. 1911	5	1.9	3R	13.6
Yeasts	85	32.3	3R	13.6
Debaryomyces hansenii (Zopf) Lodder&Kreger-van Rij 1984	15	5.7	1R	4.6
Zygowilliopsis californica (Lodder) Kudryavtsev 1960	70	26.6	1R	4.6
Total count=			**263**	
Number of genera=			**10**	
Number of species =			**27**	

Occurrence remarks (OR): H= high occurrence, between 11-22 cases (out of 22); M= moderate , between 7-10cases; L= low occurrence, between 4-6 cases; and R= rare occurrence, less than 4 cases. (F1 % = Percentage frequency of occurrence from total colonies, F2 %= Percentage frequency of occurrence from total samples). Total count = TC, number cases of isolation = NCL, occurrence remark = OR.

Table.2 Fungi isolated from Blood samples on Rose Bengal chloramphenicol agar medium.

Isolation Media	Rose Bengal chloramphenicol agar			
	TC	F 1%	NCI &OR	F 2%
Genera & species				
Acrophialophora fusispora (S.B. Saksena) Samson 1970	1	0.4	1R	4.6
Alternaria	3	1.3	1R	4.6
A. alternata(Fr.) Keissl. 1912	1	0.4	1R	4.6
A. chlamydospora Mouch. 1973	2	0.9	1R	4.6
Aspergillus	102	44.2	14H	63.6
A. flavus var. columnaris Raper& Fennell 1988	50	21.7	11H	50.0
A. flavus var. flavus Link 1809	13	5.6	5M	22.7
A. niger sensu auct. pro parte, pre 2007	27	11.7	7M	31.8
A. ochraceus G. Wilh. 1877	4	1.7	2R	9.1
A. terreus var. terreus Thom 1918	8	3.5	2R	9.1
Cladosporium	35	15.2	8M	36.4
C. cladosporioides (Fresen.) G.A de. Vries 1952	31	13.4	7M	31.8
C. oxysporum Berk. & M.A. Curtis 1868	4	1.7	1R	4.6
Fusarium oxysporum Schltdl. 1824	1	0.4	1R	4.6
Penicillium	38	16.5	8M	36.4
P. aurantiogriseum Dierckx 1901,	1	0.4	1R	4.6
P. chrysogenum Thom 1910	15	6.5	5L	22.7
P. citrinum Thom 1910	11	4.8	2R	9.1
P. crustosum Thom 1930	4	1.7	2R	9.1
P. griseofulvum Dierckx 1901	5	2.2	1R	4.6
P. pinophilum Hedgc. 1910	2	0.9	1R	4.6
Scopulariopsis	2	0.9	1R	4.6
S. candida Vuill. 1911	1	0.4	1R	4.55
S. brevicaulis Bainier 1907	1	0.4	1R	4.6
Ulocladium atrum Preuss 1852	5	2.2	2R	9.1
Yeasts	44	19.1	3R	13.6
Candida glabrata (H.W. Anderson) S.A. Mey. & Yarrow 1978	24	10.4	2R	9.1
Zygowilliopsis californica (Lodder) Kudryavtsev 1960	20	8.7	1	4.6
Total count			**231**	
Number of genera=			**9**	
Number of species =			**22**	

Table.3 Fungal distribution according to the type of cancer with blood samples.

The most common fungi	Type cancer	Percent of total isolates
A.niger	Cancer bladder	0ne isolate
A. flavus var. columnaris	Acute lymphoid leukemia (ALL)	21 %
A. flavus var. columnaris	Non-Hodgkin's lymphoma (NHL)	25.8 %
P. chrysogenum	Hodgkin's lymphoma (HL)	40 %
A. flavus var.*columnaris*	Stomach cancer	40 %
A. terreus var. *terreus*	Neuroblastoma	82 %
A. fumigatus, A.niger and *P. crustosum*	Testicular seminoma	Same percent 22 %
Candida glabrata	Tumor vertebral columnar	69 %
A.niger	Brian tumor	33.3 %

The results were almost in harmony with the findings reported by (Bodey *et al.,* 2002; Cornely *et al.,* 2015; EL-mahallawy *et al.,* 2002; Hachm *et al.,* 2008; Morgan *et al.,* 2005; Pagano *et al.,* 2001 and 2010; Patterson, 2000; Pfaller and Diekema 2004; Rath and Ansorg 1997; Ruangritchankul *et al.,* 2015; Walsh *et al.,* 2004). They indicated that the majority of moulds isolated of malignancies patients consisted of *Aspergillus, Fusarium* and Yeasts.

Our results were almost agreed with the findings of (Patterson, 2000), showed that more than 350 species that belong to the genus *Aspergillus* have been described. Only a few of them are known to be pathogenic in humans such as *Aspergillus fumigatus* which is responsible for more than 90% of invasive disease.

In addition, (Morgan, 2005), isolated different *Aspergillus* species from immunosuppressed host, and reported that *Aspergillus* can cause a variety of clinical syndromes ranging from mild, transient asthma to serious and disseminated disease.

Pagano *et al.,* (2001), reported that the *Aspergillus* was identified as the cause of FFI in 296 patients with hematologic malignancies, Mucorales in 45 patients, *Fusarium* in 6 patients and other filamentous fungi species in 4 patients, while in a further 40 patients no agent was identifiable. The overall mortality rate three months after the diagnosis of FFI was 74%, and fungal infection had been the cause of death in 51% of patients.

In addition, the results were similar with (Pagano, 2010), noted that fungal infections in these patients are mainly caused by *Aspergillus* spp and *Yeasts* less frequently than other agents may be involved such as those responsible for *Mucor*, *Rhizomucor* and *Rhizopus* spp.

On the other hand, (Pfaller and Diekema, 2004; Walsh *et al.,* 2004), reported that *Candida* species such as *C. tropicalis, C. parapsilosis* and *C. lusitaniae* had also been implicated in fungal infections in immunocompromised individuals.

In addition to (Bodey *et al.,* 2002; Cornely *et al.,* 2015; EL-mahallawy *et al.,* 2002; Hachm *et al.,* 2008; Walsh *et al.,* 2008), reported that cancer patients were vulnerable to fungal infection *Candida* spp continue to be the most common fungal pathogens in patients with cancer. They account for *Candida* spp 75 % of fungal infections, most of which have been attributed previously to *C. albicans. Candida* is the most important yeast pathogen, accounting for most invasive yeast infections (Ruangritchankul *et al.,* 2015) reported that the most common fungi, which were isolated from patients with hematologic malignancies, are *Aspergillus* spp. (58%), *Candida* spp. (16%), Mucorales (14%) and *Fusarium* spp. (10%).

In conclusion, Is clear from this study that patients with hematologic malignancies they are a suitable habitat for invasive fungi. Mould infections are mostly air borne. Contaminated water can also play a role when aerosolized (e.g. in Showers) or in cases of submersion, food, fomites and medication are less often the cause. However, health care related outbreaks do occur Immunosuppressant patients' exposure for fungal infection so should be in especial care from food, drinking and air. So we suggest that it's better to be the discovery of this fungal infection early in patients with malignancies.

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