Deep-Seated Fungal Infections in Immunocompromised Patients in Iran

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ABSTRACT

During the last two decades or so, the incidence of fungal infections has increased dramatically. Deep- seated mycoses are creating serious problems for clinicians working with certain populations of patients, such as those with cancer, the immunocompromised, and physiologically compromised.

A study of fungal isolated for identification of deep fungal infections, risk factors and etiologic agents in immunocompromised patients was carried out in the section of Medical Mycology, Pasteur Institute of Iran from 1994 to 2001. Seventy one immunosuppressed patients with deep fungal infection were retrospectively analyzed for etiology and risk factors. They had one or more predisposing factors to disseminated fungal infections. Diagnosis was established by demonstration of fungus in direct and cultural examinations. *Candida spp.* were isolated in 70.4% (39.4% *C. albicans* and 30.9% *non-albincans*), and *Aspergillus spp*. were isolated in 14.1% of cases. The most frequent risk factors were hematologic malignancy (ALL, lymphoma, Hodgkin, multiple myeloma) and diabetes mellitus. This study suggests that in immunocompromised patients, fungal infections especially in saprophytic infections, background evaluation and clinical features, correspondence of clinical symptoms and laboratory examinations should be considered and investigation of other factors which created the infection will lead us to a clear picture of patients' situation.

Keywords: Fungal Infection; Immunosuppression; Mycoses

INTRODUCTION

Fungal infections are a major cause of morbidity and mortality in the immunocompromised host. In the last 25 years, the frequency of invasive fungal infections has increased remarkably. Unbiased data concerning the true incidence and prevalence of invasive fungal infection in different patient population is limited.[1] Hart et al, reported 132 invasive fungal infections in normal and immunocompromised patients,[2] out of which 81% were caused by *Cadida SPP., Aspergillus SPP,* and *Zygomycete SPP*, Muller et al. reported the following incidence of opportunistic deep seated mycosis, candidiasis 92.6%, aspergillosis 6.7%, cryptococcosis 0.35% and zygomycosis 0.35%.[3] In a comprehensive review of invasive fungal infections, Rose and Varkey reported per 10,000 hospital discharges the following rates*: Candidia SPP*. 7.08%, *Aspergillus SPP*. 1.4%, and *Zygomycet SPP*. 0.23%.[4] Data from the National Nosocomial Infections Surveillance Program (CDC)[5] representing 1984 rates showed that *Candida SPP*. accounted for 5.5% of all isolates and was the eighth most common nosocomial pathogen.

The observed frequency of invasive fungal infections is 20-30% in patients with acute leukemia, 10-15% in patients with lymphoma, and 5% in patients with other malignancies.[6] The frequency in organ transplant recipients is 28-42% for liver, 10-35% for heart, 2-30% for bone marrow, and 0-20% for kidney.[7] Over all invasive candidiasis accounted for death in 10-40% of patients and invasive aspergillosis in 5-15%.[8]

The agents responsible for systemic fungal infections can be classified in to two groups, true

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pathogenic and opportunistic fungi. The true pathogenic fungi cause infection in normal hosts which are self-limited but in compromised hosts can be devastating. Once acquired these fungi can remain in a pseudolatent state, and disseminate when the patients becomes immunosuppressed.[9,10] The most definitive diagnostic procedure is to demonstrate the fungus in tissue by biopsy or to isolate the putative fungus in a normally sterile body fluid (Cerebrospinal fluid or blood). Many times, the former procedure cannot be done because the patient is quite ill or has potentially serious bleeding problems related to severe thrombocytopenia. These problems are most often seen in patients suspected for invasive aspergillosis and zygomycosis. Definitive diagnostic tests for disseminated candidiasis are lacking. Blood cultures are usually not helpful. Fifty percent of patients with autopsy documented disseminated candidiasis have not had a positive blood culture prior to death for *Candida SPP*. from blood.[11,12] Serologic tests, including antigen and metabolic detection, have been pursued in an effort to better diagnose disseminated candidiasis.[12,13] Concerning aspergillosis and zygomycosis definitive diagnosis is madeby demonstrating the organisms in tissue biopsies. Serologic tests for zygomycotic infections are lacking. Serologic tests for *Aspergillus* antigen are only available in research laboratories and look promising.[13] This study was conducted in order to determine deep-seated fungal infections in immuno-compromised patients.

MATERIALS AND METHODS

We retrospectively analyzed 71 immuno-compromised patients with fungal infections in Institute Pasteur of Iran between April 1994 and March 2001. The materials for investigations were collected from scrapings, crusts, and pus taken from subcutaneous abscesses or exudation from sinus tracts and biopsy specimens. Specimens for systemic mycoses were abscess, ulcer, blood, bone marrow, cerebrospinal fluid, (chest, abdominal and synovial fluid, whether aspirated or drained) eye, tissue, urine and specimens from respiratory tract include: Sputum samples, bronchial secretions, bronchial brushing, bronchial washings, alveolar lavage and lung biopsies. Identification was made by direct examination and culture. Direct preparations with the use of 10% KOH and dimethyl sulphoxide (DMSO) were made and specimens were cultured on sabouraud dextrose agar, sabouraud dextrose agar with chloramphenicol (50 mg/ml), blood agar and brain heart infusion agar (B.B.L). Duplicate cultures on each medium were incubated at 35 and 25°c regularly examined up to 4 weeks and identified using satndard methods. Microscopic features of the isolates were studied by slide culture preparation

For the purpose of yeast diagnosis, the preparations were stained using Gram's method. Identification was based on biochemical properties, the ability to produce chlamydospores and the filamentation test.

In the case of culture mould fungi (*Aspergillus, Fusarium*), positive results of mycological examinations were accepted only if the direct examination was positive and if two successive culture growths of the same fungus specimen were observed. Cases failing these criteria were regarded as negative and were not included in the study.

RESULTS

Seventy one deep fungal infections were isolated in immunocompromised patients from 1994 to 2001 (Table 1). The details of the patients and infecting organisms are given in table 2. Table 3 outlines predisposing factors to fungal infections. Seventy one deep fungal infections were isolated in patients who had one or more predisposing factors for disseminated fungal infections. Seventy one isolated fungi in immuno-compromised patients were confirmed by histology and mycological methods. Patients consisted of 31 males and 40 females and ranging in age from 7 to 80 years.

DISCUSSION

Invasive fungal infections are an increasing problem in immunocompromised patients. The most frequent mycotic infections are caused by *Candida, Aspergillus,* and *Zygomycete species*.[14-16]

Table 1. Clinical isolated organisms.

Organisms	Number	Percent
Candida spp.	50	69.4
Aspergillos spp.	10	13.9
C. neoformans	3	4.2
Fusarium spp.	2	2.8
C. bantianum	2	2.8
Acromonium	1	1.4
Peacilomyces	1	1.4
Trichosporon	1	1.4
Actinomyces spp.	2	2.8

Table 2. Characteristics of mycologically positive cases of fungal infections.

No	Sex	Age (years)	Occupation	Site Affected-Sample	Predisposing Factor	Causative Agents
1	F	65	House wife	Foot wound secretion	Diabetes Mellitus	*C. albicans*
2	M	30	Business	Lung-BAL	Tuberculosis + Systemic Lupus Erythematous	*Aspergillos sp.*
3	M	13	Student	Lung-BAL	Tuberculosis + Systemic Lupus Erythematous	*C. albicans*
4	M	49	Business	CSF	Renal Failure	*C. neoformans*
5	F	50	House wife	CSF	Hodgkin Lymphoma	*Candida sp.*
6	F	46	House wife	Vaginal-secretion	Diabetes Mellitus	*C. albicans*
7	F	65	House wife	Vaginal S.	Diabetes Mellitus	*Candida sp.*
8	F	68	House wife	Vaginal S.	Diabetes Mellitus	*Condida sp.*
9	F	60	House wife	Lung-BAL	Chronic Lymphocytic Leukemia + Chemotherapy	*C. albicans*
10	M	18	School boy	Jaw aspiration-f.	Lymphoma	*Actinomyces sp.*
11	F	46	House wife	Vaginal S.	Diabetes Mellitus	*C. albicans*
12	F	58	House wife	Sinus Maxillary biopsy	Renal Transplantation	*A. flavus*
13	F	50	House wife	Vaginal S.	Diabetes Mellitus	*C. albicans*
14	M	32	Worker	CSF	Renal Transplantation	*Candida sp.*
15	M	52	D.V.M	Buccal cavity-mucosal	Hemophilia + Antibiotic Therapy	*C. albicans*
16	M	48	Business	CSF	Diabetes Mellitus + Addiction + Asthma	*C. neoformans*
17	F	37	House wife	Lung-BAL	Diabetes Mellitus + Weight Loss	*C. albicans*
18	F	51	House wife	Lung-BAL	Immunosuppressive Therapy	*C. albicans*
19	F	35	House wife	Brain abscesses-aspiration	Diabetes Mellitus + Malignancy	*A. fumigatus*
20	F	51	House wife	Lung-BAL	Immunosuppressive Therapy	*C. albicans*
21	F	56	House wife	Lung-BAL	Renal Transplantation + Immunosuppressive therapy	*C. albicans*
22	F	61	House wife	Urinary tract-urin	Diabetes Mellitus	*Candida sp.*
23	F	38	House wife	CSF	Behcet's Syndrome	*Candida sp.*
24	F	25	House wife	CSF	Renal Transplantation	*C. neoformans*
25	F	56	House wife	Vaginal S.	Diabetes Mellitus	*C. albicans*
26	M	66	Retired	Lung aspiration	Renal Failure + Tuberculosis	*C. albicans*
27	F	31	House wife	CSF	Systemic Lupus Erythematous	*C. albicans*
28	M	53	Business	CSF	Tuberculosis + Brucellosis	*C. albicans*
29	F	10	School girl	Urinary tract	Acute Lymphocytic Leukemia	*Candida sp.*
30	F	60	House wife	Buccal Cavity mucosal	Renal Transplantation	*C. albicans*
31	M	63	Worker	CSF	Nephrectomy	*C. albicans*
32	F	55	House wife	Lung-BAL	Renal Transplantation	*Candida sp.*
33	F	62	House wife	Urinary tract-Urine	Diabetes Mellitus	*Candida sp.*
34	M	47	Business	Finger-biopsy	Diabetes Mellitus	*C. albicans*
35	F	25	House wife	Lung-BAL	Acute Lymphocytic Leukemia + Chemotherapy	*C. albicans*
36	F	49	House wife	Pritoan-fluid	Renal Failure	*Candida sp.*
37	M	57	Business	Sinus-biopsy	Multiple Myeloma	*Candida sp.*
38	M	59	Business	Palate-biopsy	Chronic Lymphocytic Leukemia	*Candida sp.*
39	M	17	Worker	Sinus-biopsy	Wegner's Syndrome	*C. bantianum*
40	M	17	Worker	Thorax-biopsy	Wegner's Syndrome	*C. bantianum*
41	F	34	House wife	Urinary tract-urine	Liver and Renal Failure	*C. albicans*
42	F	37	House wife	Lung-BAL	Diabetes Mellitus + Tuberculosis	*A. niger + c. allrincans*
43	M	47	Engineer	Lung-BAL	Chronic Lymphocytic Leukemia + Tuberculosis	*Candida sp.*
44	M	67	Unemployed	Hand-biopsy	Burning	*C. albicans*
45	M	80	Retired	Foot-biopsy	Diabetes Mellitus	*Acromonium*
46	F	78	House wife	Hand-biopsy	Diabetes Mellitus + Renal Failure	*Peacilomyeas*
47	F	59	House wife	Urinary tract-urine	Diabetes Mellitus	*Candida sp.*

Table 2. (continued)

No	Sex	Age (years)	Occupation	Site Affected-Sample	Predisposing Factor	Causative Agents
48	F	7	School girl	CSF	Acute Lymphocytic Leukemia	*C. albicans*
49	M	58	Retired	Lung-BAL	Systemic Lupus Erythematous + Immunosuppressive Therapy	*Candida sp.*
50	F	60	House wife	Urinary tract-urin	Diabetes Mellitus	*Candida sp.*
51	F	48	House wife	Genital-secretion	Diabetes Mellitus	*Candida sp.*
52	M	15	School boy	Foot-biopsy	Chronic Granulomatous Disease	*Fusarium sp.*
53	M	15	School boy	Lung-BAL	Chronic Granulomatous Disease	*Fusarium sp.*
54	F	45	House wife	Genital secretion	Diabetes Mellitus	*C. albicans*
55	F	14	School girl	Buccal-mueccos	Diabetes Mellitus	*C. albicans*
56	F	60	House wife	Lung-BAL	Diabetes Mellitus	*A. niger*
57	M	60	Retired	Lung-BAL	Chronic Lymphocytic Leukemia	*Candida sp.*
58	M	55	Retierd	Lung-BAL	Diabetes Mellitus	*C. albicans*
59	F	11	School girl	Thorax-biopsy	Chronic Granulomatous Disease	*A. fumigatus*
60	M	53	Member ship	Lung-BAL	Chronic Lymphocytic Leukemia	*C. albicans*
61	F	7	School girl	Head-abcces	Chronic Granulomatous Disease	*A. fumigatus*
62	M	32	Worker	Lung-BAL	Renal Transplantation	*C. albicans*
63	F	52	Teacher	Lung-BAL	Renal Transplantation	*C. albicans*
64	F	44	Teacher	Lung-BAL	Rheumatic Arthritis	*A. flavus*
65	F	40	House wife	Knee-biopsy	Hydatic Cyst in Knee + Surgery	*Actinomyces sp.*
66	M	13	School boy	Subcutaneous absseces-aspiration	Chronic Granulomatous Disease	*A. terreus*
67	M	41	Worker	Urinary tract-urin	Renal Transplantation	*Trichosporon*
68	M	57	Unemployed	Lung-BAL	Multiple Myeloma	*Aspergillos sp.*
69	M	57	Unemployed	Buceal Muccos	Multiple Myeloma	*Candida sp.*
70	F	86	House wife	Lung-BAL	Diabetes Mellitus	*Candida sp.*
71	M	18	School boy	Lung-BAL	Immunosuppressive Therapy	*Candida sp.*

The increased incidence correlates with intensive immunosupperssive therapy and with widespread use of broad-spectrum antibiotics.[8,10,17]

With ever expanding application of immuno-suppressive therapy, the role that host factors (the T lymphocyte system) play in the defense against systemic fungal infections is currently the subject of intensive studies, and new approaches for antifungal therapy are being investigated.[17,18]

Many host-related as well as iatrogenic factors predispose to disseminated fungal infections, including chronic debilitation, malnutrition, deficient T-cell numbers or function, hematologic malignancy, other neoplasms, rheumatic disease, chronic renal failure, burns, I.V. drug use, corticosteroid treatment, parenteral alimentation, extensive surgery, immuno-suppressive therapy after transplantation.[8,9,17]

We isolated 28.4% of fungal infections in diabetic patients. Diabetes is a common metabolic disorder with significant morbidity and mortality, and is commonly considered as a risk factor of mycoses.[19,20]

Usually in these patients, the most common fungal invasion are those of the skin, the urinary tract, and the respiratory tract.[21,22] Several studies have detected impaired phagocyte function, such as adherenc, chemotaxis, phagositosis, and bactericidal activity, especially in patients with poor metabolic control.[23,24]

Disseminated disease almost always develops

Table 3. Predisposing factors to fungal infections.

	Number	Percent
Diabetes Mellitus	25	28.4
Heamatology Malignancy	13	14.8
Renal Failure and Renal Transplantation	14	15.9
Infectious Diseases (Tubersulosis, Brucellosis)	9	10.2
Chronic Granulomatos disease (CGD)	5	5.7
Autoimmune Disease (SLE, W.G, R.A, Behcet's Syndorme)	6	6.8
Immunosuppressive Therapy	5	5.7
Antibiotic Therapy	2	2.3
Bone Marrow Malignancy	1	1.1
Others (Goitre, Addiction, Burn, Surgery, etc)	3	3.4

during periods of profound neutropenia. The frequency of prolonged neutropenia as a predisposing factor suggests that the neutrophils have a major role in host defence against fungal infections.[5] Host defence depends mostly on the phagocytic and oxidative activities of neutrophils, monocytes, and macrophages.[6,17,18]

Taken in its broadest sense, the immune system depends not only on the adequacy of cellular and humoral response against potentially harmful organisms and toxins, but also on the integrity of the skin and mucomembrane barrier that separates the individual from the outside world. Failure of one or more of these system components increases the risk of infections in general, and failure in cellular immune response and interruption of barrier integrity are the key factors specifically in the pathogenesis of most mycotic infections.[6,25]

Neutropenic patients are at the greatest risk of fungal infections of a serious nature when neutrophil cell counts drop below 1000 cells/ml and remain at these levels for 7 days or more.[14] Hematologic malignancies and chemotherapy are the usual causes of neutropenia of this degree. Ulceration of the gastrointestinal tract caused by chemotherapeutic agents used in the treatment of cancer in these patient population contributes to the problem by providing convenient portals of entry for mycotic invaders as well.[26] Corticosteroid therapy, radiation therapy, chronic granulomatous disease, and diabetes mellitus may also reduce either the number or the effectiveness of neutrophils and other phagocytes with a corresponding reduction in host resistance.[6,27]

Systemic candidiasis, aspergillosis, and Mucosal infections are the mycoses most often associated with neutropenia or impairment of phagocytic functions.[15-18] Other organisms that occasionally cause serious infections in neutropenic patients includes *Tricrosporon* and *Fusarium Spp*.[28] Fungal colonization, duration of antibiotic therapy, the number of different antimicrobial agents, fever and rash were found to be independent risk factors for fungal infection. Fungal colonization is one of the most important risk factors for invasive mycosis.[15,29]

In our study the most common predisposing factors in the patients were diabetes mellitus (28.4%), renal failure and renal transplantation (15.9%), hematologic malignancy (14.8%), corticosteroid, antibiotic and immunosuppressive, therapy (13.6%). These patients will usually have prolonged neutropenia and will have persistent fever and unresponsiveness to antimicrobial agents.

On the basis of our experience and that of others,[14,17,18,28,30] we have tried to develop some guidelines to aid this problem. A high index of suspicion must be maintained in the immunocompromised patient who has been receiving antibiotics and who has an elevated temperature either associated with pneumonia or of undermined origin, when that fever persists for 21 or more days. Particularly suspect is that group of patients who have been receiving adrenal corticosteroids as part of their chemotherapeutic regimen. For patient whose condition is in remission, the risk of further chemotherapy must be carefully weighed against its anticipated benefits; the high risk of recurrent fungal infection may preclude such therapy.[16,26]

Diagnosis must be pursued vigorously, positive *Candida* cultures given more weight, and endoscopic procedures should be undertaken in an aggressive fashion. Biopsy of lung and other organs suspected of involvement is mandatory when the patient's clinical condition permits. Platelet transfusions can be given to the thrombocytopenic patients during the procedure.[18,27] A trail of amphotericin B may be indicated in the patient who has been on steroids and who has pneumonia, prolonged fever, unresponsiveness to antibiotic therapy. Because the incidence of infections in immunocompromised patients is extremely high, it is still possible that prophylaxis is in fact early therapeutic intervention at a stage during which clinical signs of infection are still absent.

Fungal colonization, duration of antimicrobial therapy, fever and rash were recognized as important independent risk factors for fungal infection in these patients. It was also shown that the isolation of fungi from sterile body fluid (blood and cerebrospinal fluid) in standard broth for blood cultures was insufficient for the diagnosis of systemic fungal infections in patients with heamatologic malignancies during life.[31] Hart et al, reported 132 fungal infections in normal and immunocompromised patients.[2] Seventy infections occurred in immunocompromised patients (53%), Hart et al, reported 81% infections caused by *Candida spp.*, *Aspergillus spp*., and *zygomycete spp.* and 12% by *Cryptococcos spp*.[2] Muller et al. reported candidiasis 92.6%; aspergillosis 6.7%; cryptococcosis 0.35%; and zygomycosis 0.35%.[3] In our study, we found 69.4% of infections caused by *Candida spp.* and 13.9% by *Aspergillos spp.*

In addition, diabetes mellitus (28.4%), renal failure and renal transplantation (15.9%), hematologic malignancy (14.8%) corticosteroid, immunosuppressive and broad spectrum antibiotic therapy (13.6%) were considered to be higher risk factor in our study.

Finally, in immunocompromised patients with high fever for 3-5 days, no response to antimicrobial therapy, should be considered and investigated. A high degree of awareness and efforts for an early diagnosis may aid to improve the poor prognosis.

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