Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989-2003)

Georgios Chamilos
Mario Luna
Russell E. Lewis
Gerald P. Bodey
Roy Chemaly
Jeffrey J. Tarrand
Amar Safdar
Issam I. Raad
Dimitrios P. Kontoyiannis

We evaluated autopsy-proven invasive fungal infections (IFI) in patients with hematologic malignancies over three periods (1989-1993, 1994-1998, and 1999-2003). The autopsy rate declined significantly (67%-34%-26%, respectively $p<0.0001$). IFI were identified in 314 (31%) of 1017 autopsies. Most IFI (75%) were not diagnosed antemortem. The prevalence of invasive mold infections increased significantly (19%-24%-25% $p=0.05$) in parallel with the emergence of *Zygomycetes* (0.9%-4%-3%; $p=0.03$). The prevalence of all other IFI remained relatively constant. Among patients with invasive pulmonary aspergillosis, those with graft-versus-host disease had a histopathological pattern distinct from those with neutropenia. The complex and evolving epidemiology of IFI in severely immunocompromised patients is not well captured by current diagnostic methods.

Key words: autopsy, aspergillus, *Candida*, *Zygomycetes*, hematologic malignancies.

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From the Departments of Infectious Diseases, Infection Control and Employee Health (GC, REL, GB, RC, AS, IIR, DPK); Pathology (ML), Laboratory Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, TX (JJT); University of Houston College of Pharmacy, Houston, TX, USA (REL, DPK).

Correspondence:
Dimitrios P. Kontoyiannis, Department of Infectious Diseases, Infection Control and Employee Health, Unit 402, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030 USA.
E-mail: dkontoyi@mdanderson.org

Invasive fungal infections (IFI) are leading causes of death in severely immunocompromised patients.[1-3] A shift in the epidemiology of IFI has been observed over the past two decades, concomitant with an expansion of the antifungal armamentarium and a widening spectrum of immunosuppresive agents.[1] Since the early 1990s, invasive aspergillosis has become the predominant IFI,[1-3] whereas the incidence of invasive candidiasis has declined significantly in this patient population.[1,4] In recent years, several cancer centers have reported an increase in the incidence of infections caused by difficult-to-treat opportunistic molds such as *Zygomycetes*, *Fusarium*, and *Scedosporium* species and yeasts such as *Trichosporon* species.[1,3,5] Furthermore, the increasing incidence of infections caused by less antifungal-susceptible *Aspergillus* species[6,7] and azole-resistant *Candida spp.* is of concern.[1,4] Therefore, there is a need for better understanding of the complex epidemiology and immunopathogenesis of IFI.

In the present study, we sought to identify trends in the prevalence, clinical and histopathological characteristics of autopsy-proven IFI over the past two decades in patients with hematologic malignancies in our tertiary care cancer center.

Design and Methods

We identified patients with hematologic malignancies, who underwent autopsy examination at The University of Texas M.D. Anderson Cancer Center from 1-1-1989, through 12-31-2003. We evaluated patients' demographics; type and status of malignancy; type and date of hematopoietic stem cell transplantation (HSCT); risk factors for IFI (e.g., neutropenia, graft-versus-host disease [GvHD], receipt of corticosteroids); splenectomy; and intercurrent infections. Furthermore, we collected data on the fungal species identified in cultures from sterile sites, whether IFI contributed to death, and whether IFI was an incidental finding at the autopsy. An experienced pathologist (*ML*) evaluated in a blinded fashion the histopathological patterns of invasive pulmonary aspergillosis in a subset of recipients of HSCT with severe GvHD and in a subset of patients with severe neutropenia. The standardized EORTC/MSG criteria were applied for the antemortem diagnosis of IFI.[8] IFI was considered to have contributed to a patient's death if there was significant involvement of a major organ by the fungal pathogen. Severe neutropenia was defined as a neutrophil count < 100/mm^3 for longer than 10 days. Significant corticosteroid use was defined as the use of 600 mg of a prednisone equivalent during the month prior to the diagnosis of the IFI.

We analyzed trends in the prevalence and clinical characteristics of IFI over three 5-year periods (A, 1989-1993; B, 1994-1998; C, 1999-2003) by using the 3×2 χ^2 test. Continuous variables were analyzed using the Mann-Whitney U test. A p value ≤0.05 was always considered statistically significant.

Results and Discussion

Demographics and characteristics of patients with IFI

In a total of 1017 autopsy examinations, 314 (31%) IFI were identified (Table 1). The autopsy rate (autopsies/deaths) declined continuously (A, 63%; B, 35%; C, 27%;

Table 1. Demographics and clinical characteristics of the patients with IFI.*

Characteristic	No. of patients (%) 1989-1993	1994-1998	1999-2003	p value
Male	87/147(59)	54/85 (64)	41/82 (50)	0.1900
Median age, years (range)	44 (15-87)	49 (2-83)	53 (19-77)	0.1500
Acute myelogenous leukemia	60/147 (41)	41/85 (48)	30/82 (37)	0.2900
Acute lymphoblastic leukemia	23/147 (16)	16/85 (19)	17/82 (21)	0.3700
Chronic myelogenous leukemia	25/147 (17)	5/85 (6)	5/82 (6)	0.0070
Non-Hodgkin's lymphoma	15/147 (10)	9/85 (11)	9/82 (11)	0.9800
Chronic lymphocytic leukemia	8/147 (5)	3/85 (4)	9/82 (11)	0.1000
Myelodysplastic syndrome	8/147 (5)	5/85 (6)	6/82 (7)	0.7500
Other	8/147 (5)	6/85 (7)	5/82 (6)	0.6100
Allogeneic HSCT‡	43/137 (31)	30/88 (34)	26/102 (25)	0.6300
Matched related§	7/15 (47)	15/29 (52)	12/24 (50)	0.6800
Mismatched or unrelated	8/15 (53)	14/29 (48)	12/24 (50)	0.9500
Severe neutropenia	29/43 (67)	17/30 (57)	17/26 (65)	0.9300
Significant corticosteroid use	24/43 (56)	19/30 (63)	20/26 (77)	0.2000
Active GvHD (grade III-IV)	23/43 (53)	16/30 (53)	15/26 (58)	0.9300
Active malignancy	23/43 (53)	15/30 (50)	15/26 (58)	0.8400
Autologous HSCT	8/147 (5)	1/85 (1)	4/82 (5)	0.6300
Severe neutropenia	132/147 (90)	69/85 (81)	57/82 (70)	0.0070
Significant corticosteroid use without history of GvHD	8/166 (5)	39/85 (46)	26/82 (32)	<0.0001
Active malignancy	108/147 (73)	68/85 (80)	70/82 (85)	0.0700
IFI incidental autopsy finding‖	20/147 (14)	9/85 (11)	4/82 (5)	0.7800
IFI undiagnosed antemortem	123/147 (84)	57/85 (67)	55/82 (67)	0.0030
IFI related to the cause of death	113/147 (77)	68/83 (82)	60/82 (73)	0.5700
Concomitant CMV infection	10/147 (7)	11/85 (13)	3/82 (4)	0.0600
Concomitant bacterial infection¶	37/147 (25)	58/85 (68)	37/82 (45)	<0.0001
Autopsy rate (autopsies/deaths)#	466/739 (63)	283/808 (35)	268/987 (27)	<0.0001

Three hundred and sixty-five fungal pathogens were isolated because of 44 mixed IFI; ‡in seven allogeneic HSCT recipients, the diagnosis of IFI was not suspected antemortem; §three HSCT recipients received a non-myeloablative conditioning regimen; ‖ the prevalence of Candida spp. identified incidentally at autopsy (16/113, 14%) was significantly higher than that of Aspergillus spp. (10/178, 6%) (p=0.01; OR, 2.7; 95% CI, 1,2-6.3); ¶ most concomitant bacterial infections were caused by Staphylococcus spp. (24 coagulase-negative staphylococci, 10 Staphylococcus aureus isolates), Enterococcus spp. (n=26), Stenotrophomonas maltophilia (n=14), Pseudomonas aeruginosa (n=12), and Klebsiella spp. (5 Klebsiella pneumonia, 1 Klebsiella oxytoca); #there were 12 patients with a history of splenectomy and IFI, which were caused by Aspergillus spp. (n = 5), Zygomycetes spp. (n=3), Candida spp. (n = 4), Fusarium spp. (n=1), or Cryptococcus neoformans (n=1). Of the patients who underwent splenectomy, four had chronic myelogenous leukemia, four had chronic lymphocytic leukemia, two had Hodgkin's disease, one had acute myelogenous leukemia, and one had acute lymphoblastic leukemia; three patients who underwent splenectomy were HSCT recipients.

p<0.0001). Most IFI (242 [77%]) occurred in patients with leukemia and most IFI were found in patients with active malignancy (246 [78%]). The proportion of patients with IFI who had severe neutropenia decreased after period A (A, 90%; B, 81%; C, 70%; p=0.007). In contrast, the percentage of patients with IFI who had received a significant dose of corticosteroids irrespectively of GvHD increased significantly (A, 5%; B, 46%; C, 32%; p<0.0001). Of interest, 12 patients with IFI had a history of splenectomy caused by uncommon molds such as *Zygomycetes* and *Fusarium spp.*; most of these patients (10 [83%]) had malignancies normally at low risk for the development of IFI. IFI were frequent in allogeneic HSCT recipients who underwent autopsy (99/327 [30%]). All but one of these patients had a history of severe GvHD (35/99; 35%) or severe neutropenia, (44/99; 44%) or both severe GvHD and severe neutropenia (19/99; 19%). IFI were typically diagnosed late after transplantation (> 100 days) in HSCT recipients with severe GvHD (30/46 [65%]). The vast majority of the IFI (241 [77%]) contributed significantly to patients' death. Importantly, only 25% of the IFI were diagnosed antemortem as proven or probable IFI according to the EORTC/MSG criteria. Nonetheless, the rate of antemortem diagnosis of IFI improved over the last two study periods (p=0.003).

Table 2. Trends in the prevalence of IFI.

Fungal pathogen	Prevalence of IFIs (%) 1989-1993	1994-1998	1999-2003	p value
IFI*	147/466 (32)	85/283 (30)	82/268 (31)	0.900
Invasive mold infections	89/466 (19)	67/283 (24)	68/268 (25)	0.050
Candida†	62/466 (13)	28/283 (10)	23/268 (9)	0.070
C. albicans	15/466 (3.2)	8/283 (2.8)	5/268 (1.8)	0.500
Non-*albicans* *Candida spp.*	15/466 (3.2)	19/283 (6.7)	21/268 (7.8)	0.010
C. krusei	2/466 (0.4)	8/283 (2.8)	7/268 (2.6)	0.010
C. glabrata	7/466 (1.5)	7/283 (2.4)	7/268 (2.6)	0.500
C. parapsilosis	1/466 (0.2)	0/283 (0.0)	1/268 (0.4)	0.600
C. tropicalis	5/466 (1.0)	4/283 (1.4)	2/268 (0.7)	0.700
Other Candida spp.‡	0/466 (0.0)	0/283 (0.0)	4/268 (1.4)	0.004
Aspergillus	73/466 (16)	54/283 (19)	51/268 (19)	0.360
A. fumigatus	3/466 (0.6)	6/283 (2.1)	8/268 (2.9)	0.040
Non-fumigatus aspergilli	14/466 (3.0)	8/283 (2.8)	14/268 (5.2)	0.220
A. flavus	8/466 (1.7)	3/283 (1.0)	7/268 (2.6)	0.380
A. terreus	4/466 (0.9)	5/283 (1.7)	6/268 (2.2)	0.290
Other *Aspergillus spp.*	2/466 (0.2)	0/283 (0.0)	1/268 (0.4)	0.550
Scedosporium spp.	1/466 (0.2)	1/283 (0.4)	2/268 (0.7)	0.530
Fusarium spp.	4/466 (0.9)	2/283 (0.7)	4/268 (1.4)	0.600
Culture-negative hyalohyphomycetes	62/466 (13)	40/283 (14)	32/268 (12)	0.730
Zygomycetes	4/466 (0.9)	10/283 (4.0)	8/268 (3.0)	0.030
Pneumocystis jiroveci pneumonia	9/466 (1.9)	1/283 (0.4)	1/268 (0.4)	0.050
Mixed infections	17/164(10)	14/96(15)	13/94(14)	0.540
Mixed *Candida/Aspergillus*	11/135 (8)	9/82 (11)	9/74 (12)	0.600

**there were also three Histoplasma capsulatum, two Trichosporon beigelii, one Rhodotorula species, and one C. neoformans infection; †thirty-seven Candida isolates were not identified at the species level, and five cases of mixed infections were caused by more than two Candida spp.; ‡two Candida guillermondii, one Candida lusitaniae, and one Candida kefyr species were identified at autopsy.*

Trends in the prevalence of fungal pathogens

Overall, the prevalence of IFI remained high and constant across the study periods (A, 32%; B, 30%; C, 31%; p=0.9) (Table 2, Figure 1). However, there was an increase in the prevalence of invasive mold infections (A, 19%; B, 24%; C, 25%; p=0.05), in parallel with the

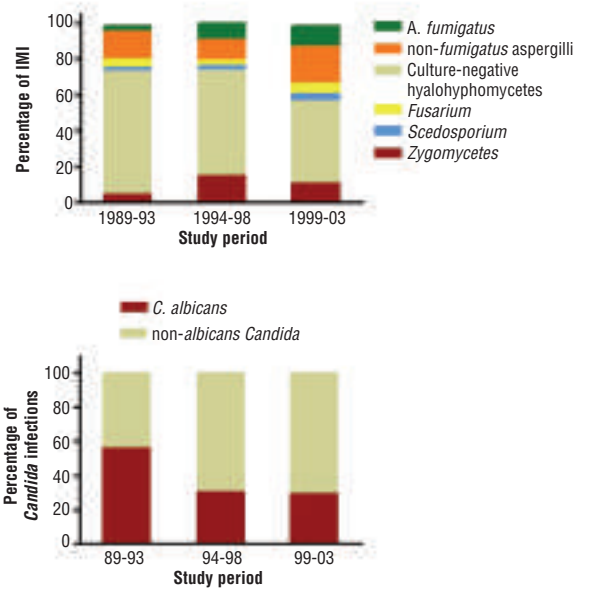

Figure 1. Spectrum of (A) invasive mold infections (IMI) and (B) invasive *Candida* infections over time.

emergence of zygomycosis after period A (A, 1%; B, 4%; C, 3%; p=0.03). The prevalence of invasive aspergillosis, the predominant IFI in each study period, remained stable (A, 16%; B, 19%; C, 19%; p=0.36). *A. flavus* (n=18) and *A. terreus* (n=15) accounted for the majority (62%) of the cases of culture-proven aspergillosis from the early years of the study. Culture-negative hyalohyphomycetes (*Aspergillus* versus *Fusarium* versus *Scedosporium spp.*) accounted for approximately two thirds (134 [60%]) of all invasive mold infections. The rate of invasive candidiasis decreased over the three study periods (A, 13%; B, 10%; C, 8%; p=0.07). *Candida spp.* other than *C. albicans* (mainly *C. krusei* and *C. glabrata*) became the main *Candida spp.* after period A (p=0.01).

Histopathological characteristics of invasive pulmonary aspergillosis in autopsy examinations

The histopathological pattern of invasive pulmonary aspergillosis in HSCT recipients with GvHD differed from that in neutropenic patients, consisting of severe lung inflammation (5/7 [71%] versus 0/18 [0%]; p=0.0004) and less abundant *Aspergillus* burden (Table 3). In contrast, in all patients with neutropenia, the histopathology of invasive pulmonary aspergillosis was characterized by scant inflammation, hyphal angioinvasion with a high fungal burden, and extensive coagulative tissue necrosis. However, as opposed to the animal model of invasive pulmonary aspergillosis,[9,10] in which dissemination of *Aspergillus spp.* occurred exclusively in neutropenic and not in corticosteroid-treated mice, both patient cohorts had an equally high prevalence of disseminated invasive aspergillosis.

Herein we report on the largest single-institution study of autopsy-proven IFI in patients with hematologic malignancies spanning two decades. Alarmingly, and consistently with reports from other institutions, there was a continuous and significant decline in the autopsy rate.[11] In agreement with previous surveys,[12-14] we observed a high prevalence of IFI (31%) at autopsy in this population of patients. Whereas most of the IFI (77%) were significantly related to the patients' death, less than one third of them were diagnosed antemortem by EORTC/MSG criteria, this too compatible with recent reports by other investigators.[15]

In correlation with previous studies, we found that patients with acute leukemia and recipients of allogeneic HSCT were at the highest risk of IFI.[1-4] Furthermore, the majority of these patients had active malignancies and multiple risk factors for IFI. Of interest, the increased number of patients who had received significant doses of corticosteroids irrespectively of GvHD may reflect changes in the management of cancer at our institution over the past decade.

Importantly, we found an increased prevalence of IFI caused by uncommon molds in low-risk patients who had previously undergone splenectomy. Several studies indicate an association between splenectomy and IFI.[16,17] However, only case-control studies can address whether splenectomy is an independent risk factor for IFI.

Our study revealed that invasive mold infections are the predominant IFI in patients with hematologic malignancies in our institution. In accordance with reports from other oncology centers,[3] *Zygomycetes* infections have increased in our institution since 1994.[5] As in previous autopsy studies,[12-14] we observed a decreasing trend in the prevalence of *Candida* infections. However, in contrast with these studies, which reported a 3-fold increase in the prevalence of invasive aspergillosis at autopsy over the past two decades,[12-14] the prevalence of invasive aspergillosis in our institution was relatively

Table 3. Univariate analysis of histopathological characteristics in autopsy examinations of recipients of HSCT with severe GvHD as compared with leukemia patients with severe neutropenia.

Histopathological pattern	*HSCT recipients with severe GvHD**	*Patients with leukemia with severe neutropenia†*	*Univariate analysis*	
			OR (95% CI)	*p value*
Inflammatory (PMN infiltration)	5/7 (71%)	0/18 (0%)	81.4 (3.3-1963)	0.0004
Coagulative necrosis (non-inflammatory)	2/7 (29%)	18/18 (100%)	–	
Median lung weight, g (range)	900 (600-1300)	1200 (900-1900)	–	0.0400
Disseminated invasive pulmonary aspergillosis	5/7 (71%)	11/14 (79%)	–	0.6700

*PMN: polymorphonuclear leukocyte. *Five of the 11 available HSCT recipients with severe GvHD also had neutropenia at the time of diagnosis of invasive pulmonary aspergillosis and were excluded from the analysis; †two of the 19 available patients with severe neutropenia received white blood cell transfusions and high doses of systemic corticosteroids during the month prior to the diagnosis of invasive pulmonary aspergillosis and were excluded from the analysis. In addition, one of the patients had concomitant Pseudomonas pneumonia.*

stable. We also found that non-*fumigatus* aspergilli, including *A. terreus* and *A. flavus*, were the main *Aspergillus spp*. during the study. Importantly, these species have been increasingly recognized as opportunistic pathogens in several cancer centers.[6,7,18] The predominance of non-*fumigatus* aspergilli may be, at least partially, a reflection of antifungal selection pressure.[7] Alternatively, because non-*fumigatus* aspergilli are a frequent cause of nosocomial infections, an epidemiological niche for these species may also account for their predominance in some institutions.[6,18] Importantly, culture-negative *hyalohyphomycetes* accounted for a significant proportion (60%) of invasive mold infections. The low yield of positive cultures at autopsy in our study corroborates the results described in previous reports.[19]

We also compared the histopathology of invasive pulmonary aspergillosis in recipients of HSCT with GvHD and patients with severe neutropenia. As recently reported for animal models, we observed distinct patterns, suggesting that there are differences in the pathophysiology of invasive pulmonary aspergillosis.[9,10] However, in contrast to the animal model, and in agreement with other investigators,[20] disseminated invasive pulmonary aspergillosis occurred at the same frequency in both of our groups of patients, implying that the pathophysiology of this infection in these patients is complex. Despite an expanding antifungal armamentarium, IFI remain a common problem in patients with hematologic malignancies. Our study reveals that the epidemiology of IFI in such patients is complex and evolving and is not captured by the existing diagnostic methods. Future efforts should be directed at improving molecular methods of diagnosing IFI and increasing autopsies rates.

DPK was responsible for the design of study, supervision of data collection, data analysis, and writing the manuscript; GC was responsible for data collection, data analysis and writing the manuscript with DPK; GC and DPK assume primary responsibility for it; REL was responsible for data interpretation, data analysis, and critical revision of the manuscript; ML and JT were involved in the laboratory investigations, interpretation of the data and critical revision of the manuscript; GPB, RC, AS and IIR were involved in critical revision of the manuscript.

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