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CONCURRENT LUNG INFECTIONS IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES AND INVASIVE PULMONARY ASPERGILLOSIS: HOW FIRM IS THE *ASPERGILLUS* DIAGNOSIS?

Sarah P. Georgiadou, MD and **Dimitrios P. Kontoyiannis, MD**
Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030

Summary

Background—Immunocompromised patients with hematological malignancies and/or recipients of hematopoietic stem cell transplants are constantly exposed to several fungal, bacterial, and viral respiratory pathogens.

Methods—We retrospectively evaluated all patients with invasive pulmonary aspergillosis (IPA) and underlying hematological malignancies for the presence of concurrent, microbiologically documented pulmonary infections during a 5-year period (2005–2010).

Results—We found 126 such patients that frequently had coinfections (49%) with respiratory pathogens other than *Aspergillus* species, with a higher rate in patients with probable IPA (53%) than in those with proven IPA (29%; $P = .038$).

Conclusions—As the majority of patients with IPA in daily practice have probable IPA, often according to only the combination of positivity for serological biomarkers and radiological findings, our data may raise skepticism about both the certainty of IPA diagnosis and the evaluation of response to antifungals in a subset of these patients.

Keywords

Aspergillus; pulmonary; coinfection; immunocompromised; hematologic

Introduction

Pneumonia caused by opportunistic molds, *Aspergillus* species being the most common, is the most frequent and life-threatening manifestation of invasive mold infections (IMIs) in chronically immunosuppressed patients with hematological malignancies and/or recipients of hematopoietic stem cell transplants (HSCTs).[1] Such patients are constantly exposed to

Reprints or correspondence: Dr. Dimitrios P. Kontoyiannis, Department of Infectious Diseases, Infection Control and Employee Health, Unit 402, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Telephone: (713) 792-6237; Fax: (713) 745-6839 (dkontoyi@mdanderson.org).

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several fungal, bacterial, and viral respiratory pathogens[1]. The frequency, spectrum, and implications of coinfections in patients with lung IMIs have yet to be sufficiently addressed in clinical trials that typically enroll patients without major comorbidities. Limited data are derived from previous, single-institution studies [1–10] with a wide range of lung coinfection incidence. To that end, we retrospectively reviewed our 5-year experience regarding the prevalence of coinfections in patients with invasive pulmonary aspergillosis (IPA) at a large tertiary-care cancer hospital.

Patients and Methods

The electronic medical records of all consecutive patients with IPA and underlying hematological malignancies seen at The University of Texas MD Anderson Cancer Center from September 1, 2005, to September 1, 2010, were retrospectively reviewed for the presence of concurrent, microbiologically documented pulmonary infections. All the patients met the criteria for proven or probable IPA according to the revised definitions of the European Organization for Research and Treatment of Cancer (EORTC) and Mycoses Study Group (MSG).[11] Identification of molds was based on standard morphological criteria.[12] Coinfection was classified as definite if one or more pathogens were isolated from bronchoalveolar lavage (BAL) fluid or sterile samples (such as lung tissue and pleural fluid); coinfection was classified as probable if one or more pathogenic organisms were isolated from a sputum sample of sufficient quality (fewer than 15 squamous epithelial cells per low-power field) concurrently or within 7 days before or after the IMI diagnosis according to previous recommendations.[13] Organisms associated with probable colonization or sample contamination, such as coagulase-negative *Staphylococcus*, *Candida* species, *Penicillium* species, *Mycobacterium gordonae* were excluded. Coinfection was characterized as polymicrobial if two or more pathogens other than *Aspergillus* spp. were isolated and mixed if two or more types of pathogens (e.g., viruses, bacteria, fungi) were isolated. The patients' records were reviewed for demographic characteristics, underlying disease, laboratory parameters, and chest computed tomography (CT) findings. Neutropenia was defined as a neutrophil count less than 500/mm^3. *Aspergillus* galactomannan (GM) antigen assay (Platelia *Aspergillus*; Bio-Rad Laboratories, Hercules, CA) results were also recorded. The study protocol was approved by The MD Anderson Cancer Center Board and written informed consent was obtained from every patient.

Results

We identified 163 patients with underlying hematological cancers and *Aspergillus*-positive cultures of upper or lower respiratory tract samples. Of these cases, 126 met the EORTC/MSG criteria for IPA. Twenty-one patients (17%) had proven IPA, and 105 (83%) had probable IPA. The median patient age at diagnosis was 61 years (range, 12–84 years), and 72 patients (57%) were male. Acute leukemia was the most common underlying disease (48%; acute myelogenous leukemia in 36%, acute lymphocytic leukemia in 12%); 53 (42%) of the patients were HSCT recipients (48 allogeneic). The most prevalent specified *Aspergillus* species was *Aspergillus fumigatus* (45 [36%]) followed by *Aspergillus flavus* (22 [17%]). Thirty-two patients (25%) were neutropenic for an average duration of 20 days prior to IPA diagnosis (range, 1–300 days). BAL fluid was the most common source of *Aspergillus*-positive cultures (70%) followed by sputum (17%) and lung tissue (11%).

In 62 patients (49%), a second non-*Aspergillus* pathogen (bacterial, viral or fungal) was isolated; of these patients, 48 (77%) had proven coinfections, and 14 (23%) had probable coinfections. Fifty-three percent of the 105 patients with probable IPA presented with concomitant infections, compared to only 29% of the 21 patients with proven IPA ($P = .038$). Regarding the type of coinfection, 22% of the patients had bacterial coinfections (78%

of the isolated pathogens were gram-negative rods), 10% had viral coinfections, 3% had coinfections with another mold, 3% had mycobacterial coinfections, and 11% had mixed coinfections (at least two types of pathogens). Twenty patients (16%) had polymicrobial infections. There was no significant difference in the rates of coinfection in cases of IPA caused by *A. fumigatus* and non-*fumigatus Aspergillus* spp. (22/45 [49%] for *A. fumigatus*, 36/69 [52%] for non-*fumigatus Aspergillus* spp.; $P = .85$) (Table 1), the rate of neutropenia at the time of IPA diagnosis (15/32 [47%] in neutropenic patients, 47/94 [50%] in nonneutropenic patients; $P = .76$) and the sample source used for IPA diagnosis (57% of patients in whom *Aspergillus* spp. grew in sputum had coinfections, whereas 51% of those in whom *Aspergillus* spp. grew in BAL fluid; $P = .64$) (Table 2).

The serum GM antigen assay was positive in 25 (35%) of the 72 patients with IPA who underwent this assay. Nevertheless, there was no statistically significant difference in positivity between patients with and without coinfections (28% and 42%, respectively; $P = .21$). The mean ± standard deviation of GM index level was 2.02 ±1.62 in patients without coinfection versus 1.63 ±1.54 in patients with coinfection ($P=.59$). Antimicrobial treatment with β-lactams was given in 62% of all 126 patients with IPA. Chest CT scans were available for 120 of the 126 patients upon diagnosis of IMI. The most prevalent radiological finding was nodules (80 [67%]) followed by consolidation or a mass (62 [52%]). Halo signs and cavities were uncommon (12% and 13%, respectively). Likewise, there was not any significant difference in the radiological findings between patients with and without concomitant infections (Table 2).

Statistical analysis

Categorical variables were compared using the chi-square test, and continuous variables were compared using the Student t-test. All comparisons were unpaired, and tests for significance were two-tailed; P values less than 0.05 were considered indicative of statistical significance.

Discussion

In this retrospective study, we identified a high incidence rate (49%) of lung coinfections in patients with hematological malignancies and IPA. The most common type of coinfection was bacterial (22%), followed by mixed (11%) and viral (10%) coinfections. Polymicrobial pneumonia developed in a small yet sizeable subset of the IPA patients (16%). In previous studies, we had also reported the presence of concomitant infections, at a wide range (21–83%), mainly bacterial (15–54%) in patients with a variety of IMIs.[3, 6, 7, 10]

The high prevalence of coinfection in immunocompromised patients with hematological malignancies and IPA was also shown by other studies; For example, in pediatric patients with IPA, the rate of coinfection ranged from 38% to 70%,[2, 5, 8] whereas in autopsy studies of patients with hematological malignancies and invasive fungal infections, the rate of bacterial coinfection ranged from 36% to 50%.[1, 4, 9] Moreover, IPA was the most common cause of community-acquired pneumonia with gram-negative bacilli as copathogens in 60% of patients in a retrospective study of HSCT recipients with graft-versus-host-disease.[14] Furthermore, other retrospective studies of cancer patients with nocardiosis and *Legionella* pneumonia identified concurrent mold infections in 26% and 11% of the patients, respectively.[15, 16]

Most of the evidence gathered in randomized controlled trials is of limited value in guiding decisions about medication use by patients with multiple chronic diseases.[17] Likewise, most of prospective or retrospective, multiple or single-institution studies regarding antifungal

treatment, primary,[18–20] salvage,[21–26] or both,[27–29] in patients with IPA have not reported on patients with coinfections. As in several previous clinical trials, the majority of our patients had probable (83%) rather than proven (17%) IPA;[18–20, 22, 24, 25, 27, 29] in some of these studies, the diagnosis of probable IPA frequently was based only on positive GM serum assay and CT findings.[18, 19] Kinetics of GM serum assay have, of note, been recently proposed as a diagnostic tool of early response assessment in patients with IPA during clinical trials.[30] Interestingly, in the present study a higher incidence rate of coinfection was identified in patients with probable IPA than in those with proven IPA ($P = .038$), although the number of patients with proven IPA was probably low to draw safe conclusions.

IPA diagnosis remains a challenge, and current diagnostic strategies are not robust in establishing a definite diagnosis.[31, 32] Firm IPA diagnosis is further compromised in cases of probable concomitant infections for various reasons. First, CT signs in patients with IPA are not pathognomonic, and "typical" imaging findings, such as nodules and the halo sign, may be misleading, as a wide spectrum of diseases, including infections by bacterial, viral, and fungal pathogens, are occasionally associated with them.[33] In addition, several CT findings common in neutropenic patients, such as consolidation-or-mass, the halo sign, and the angioinvasive form are less common in nonneutropenic patients, in whom radiological findings are sometimes nonspecific.[34]

Non-culture-based diagnostic methods, such as GM detection and β-(1,3)-D-glucan (BG) assays, do not also have sufficient sensitivity or specificity for routine clinical use, especially in nonneutropenic patients with hematological malignancies, and their use is characterized by many false-positive results.[31, 32, 35] In a recent prospective study, investigators found false-positive GM assay results in both serum and BAL fluid samples and that these results were associated with the use of all β-lactams (not just amoxicillin-clavulanate and piperacillin-tazobactam), antibiotics commonly used in clinical practice.[36] In addition, authors have reported false-positive GM and BG assay results in patients with bacteremia, attributed to *Pseudomonas* species and other gram-negative bacteria that are frequently isolated from the blood of immunocompromised patients.[37–39] GM assay has also demonstrated cross-reactivity with several other non-*Aspergillus* molds, which may be another drawback regarding the specificity of this test. [40, 41]

Moreover, an ever-declining autopsy rate in institutions with patient populations at high risk for IMIs [Kontoyiannis, submitted] inhibits the establishment of a definitive IPA diagnosis and discrimination between colonization and invasive infection. [1] Given the severe underlying conditions that predispose patients with hematological malignancies to IPA, differentiating deaths caused by fungal disease or other coinfections from those associated with the underlying disease or drug toxicity without performing autopsy studies is often difficult.

Although our clinical data are descriptive we believe that they may raise important questions for future studies in pathogenesis and diagnostics of IPA. Specifically, BG or GM positivity (without microbiological culture confirmation), even in a highly immunocompromised host with evidence of pulmonary disease, may not always be a sufficient marker of probable IPA for inclusion in clinical trials determining antifungal regimen efficacy; Physicians should perform further diagnostic evaluation using BAL or CT-guided lung biopsy for pathogen isolation using both conventional and molecular detection methods. Regarding the diagnostic yield of BAL fluid in patients with hematological malignancies and pulmonary infections, authors reported a high incidence of polymicrobial infection (53%) in tests using standard and polymerase chain reaction-based techniques.[42] In addition, a recent study showed that computed tomographic pulmonary angiography is a promising tool for detecting vessel interruption in cases of angioinvasion associated with IMIs.[43] Finally, our data

challenge the notion, derived mainly from studies of monomicrobial infections in murine models,[44, 45] on whether single-pathogen molecular "signatures" or serum cytokine profile[46] would be diagnostically useful in real life, at least in heavily immunocompromised patients with hematological malignancies.

The pathophysiological implications of coinfections are multiple. The synergistic or sequential action of several pathogens may further attenuate compromised local and systemic immune responses and enhance the pathogens' virulence, protect them from the action of antinfectives and promote the antibiotic resistance of each copathogen.[47] Researchers have described diverse physical interactions between bacteria and fungi in vitro, ranging from bacterial cell contact and aggregation with fungal hyphae or yeast cells to organized bacterial biofilms on the surfaces of fungal hyphae.[47, 48] Furthermore, using animal models, investigators have demonstrated that in those with *Pseudomonas aeruginosa* pneumonia, recruited phagocytes are major targets of ExoU intoxication in the lung, resulting in inhibition of the ability of these cells to eradicate *P. aeruginosa.* [49] This localized impairment of an essential component of the innate immune response generates an environment of immunosuppression in the lungs of infected animals, rendering them susceptible to coinfections with other pathogens that are normally effectively controlled by the host's immune system.[49] Finally, investigators have shown that patients who die of sepsis may have biochemical, flow cytometric, and immunohistochemical findings consistent with organ-specific immunosuppression,[50] which also could heighten susceptibility to opportunistic infections such as IPA. Lately, several diseases are becoming increasingly recognized as true polymicrobial infections; however the biological relevance of microbial interactions remains largely unknown.[51]

In summary, coinfections are common in immunocompromised patients with hematological malignancies and IPA and may influence the diagnostic certainty regarding IPA diagnosis including both diagnostic biomarkers and radiological findings. In addition, the appropriateness of antifungal treatment of IPA in clinical trials and prognosis has yet to be elucidated and requires careful study. We believe that in cases of probable IPA in which respiratory copathogens are identified, physicians should likely obtain information about the appropriateness of anti-infective therapy for coinfections and exercise extra effort in establishing the certainty of IPA diagnosis, especially if IPA diagnosis is based on a biomarker alone.

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Table 1

Prevalence of Pulmonary Coinfections and Types of Copathogens According to *Aspergillus* Species in 126 Patients with IPA (EORTC/MSG Criteria)

Mold	Coinfections, *n* (%)	Copathogens*
Aspergillus fumigatus (*n* = 45)§	22 (49)	CMV (6), *Pseudomonas aeruginosa* (5), *Staphylococcus aureus* (3), *Aspergillus niger* (3), *Stenotrophomonas maltophilia* (2), *Mycobacterium intracellulare* (2), *Aspergillus terreus* (1), *Aspergillus nidulans* (1), *Mycobacterium fortuitum* (1), *Mycobacterium avium* (1), *Fusarium* species (1), *Acinetobacter* species (1), *Hemophilus* species (1), *Hafnia* species (1), *Alcaligenes* species (1), *Klebsiella pneumonia* (1), *Paecilomyces* species (1), *Scedosporium* species (1)
Aspergillus non-*fumigatus* spp. (*n* = 69)§	36 (52)	
A. flavus (*n* = 22)	12 (55)	*Stenotrophomonas maltophilia* (5), *Pseudomonas aeruginosa* (3), RSV (2), *Aspergillus fumigatus* (1), *Serratia marcescens* (1), *Enterobacter* species (1), *Neisseria elongata* (1), *Achromobacter* species (1), CMV (1), Adenovirus (1), Parainfluenza virus type 3 (1)
A. niger (*n* = 19)	10 (53)	*Hemophilus* spp. (2), *Mycobacterium avium* (2), *Mycobacterium abscessus* (1), CMV (1), *Staphylococcus aureus* (1), group B-*Streptococcus hemolyticus* (1), *Escherichia coli* (1)
A. terreus (*n* = 15)	7 (47)	*Staphylococcus aureus* (2), *Pseudomonas aeruginosa* (1), *Aspergillus nidulans* (1), A*spergillus fumigatus* (1), *Nocardia* species (1), Influenza A virus (1), RSV (1), CMV (1), Parainfluenza virus type 1 (1)
A. versicolor (*n* = 7)	4 (57)	Influenza A (2), *Fusarium* spp. (1), *Nocardia* spp. (1), *E. coli* (1)
A. nidulans (*n* = 4)	1 (25)	*Pseudomonas aeruginosa* (1)
A. glaucus (*n* = 2)	2 (100)	*Stenotrophomonas maltophilia* (1), *Pseudomonas aeruginosa* (1), *Hemophilus* spp. (1), *Mycobacterium avium* (1), Parainfluenza virus type 1 (1)
Aspergillus spp**. (*n* = 12)	4 (33)	*Staphylococcus aureus* (1), *Pseudomonas aeruginosa* (1), *Pseudomonas putida* (1), Parainfluenza virus type 3 (1)

NOTE. CMV, cytomegalovirus; RSV, respiratory syncytial virus.

* several patients had more than one copathogens.

** not specified.

§ *P* value = .85

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Table 2

Demographic, Clinical, and Radiological Characteristics of IPA Patients

	n (%)		
Characteristic	**IPA only (*n* = 64)**	**Concurrent pulmonary infection (*n* = 62)**	***P***
Sex			.570
Male	35 (55)	37 (60)	
Race			.260
White	49 (77)	53 (86)	
Other[a]	15 (23)	9 (14)	
Age, years (mean ± SD)	57 ± 14	59 ± 13	.370
Hematological malignancy			.610
AML/MDS	26 (41)	23 (37)	
ALL	8 (12)	7 (11)	
NHL/HD	14 (22)	10 (16)	
CLL	10 (16)	16 (26)	
Other[b]	6 (9)	6 (10)	
Source of mold culture			.640
BAL	43 (67)	45 (73)	
Sputum	9 (14)	12 (19)	
Prior chemotherapy[c]	36 (56)	24 (39)	**.049**
Prior corticosteroid use[d] (>600 mg)	11 (17)	10 (16)	1.000
Prior immunosuppressive therapy[c,e]	30 (47)	28 (45)	.850
Hematopoietic transplant[f]	27 (42)	26 (42)	.970
GVHD	18 (28)	18 (29)	1.000
Neutropenia (<500/mm^3)	17 (27)	15 (24)	.760
Monocytopenia (<100/mm^3)	30 (47)	21 (34)	.140
Lymphopenia (<500/mm^3)	41 (64)	33 (53)	.220
Status of malignancy[g]	(*n* = 33)	(*n* = 27)	1.000
Remission	20 (61)	17 (63)	
Active	13 (39)	10 (37)	
Radiological findings (*n* = 120)	(*n* = 61)	(*n* = 59)	
Nodule[h]	43 (70)	37 (63)	.440
Consolidation-or-mass[i]	31 (51)	31 (52)	.850
Halo sign	10 (16)	4 (7)	.150
Cavitation	10 (16)	5 (8)	.270
Air-crescent sign	1 (2)	0	--
Tree-in-bud	2 (3)	3 (5)	.680

NOTE. SD, standard deviation; AML, acute myeloblastic leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; HD, Hodgkin disease; CLL, chronic lymphocytic leukemia; GVHD, graft-versus-host-disease.

[a] Hispanic (*n* = 12), black (*n* = 9), or Asian (*n* = 3).

[b] Multiple myeloma (n = 8), chronic myelogenous leukemia (n = 3), and aplastic leukemia (n = 1).

[c] In the 2 months prior to IPA diagnosis.

[d] In the month prior to IPA diagnosis.

[e] Immunosuppressive regimens such as tacrolimus and tumor necrosis factor inhibitors

[f] Allogeneic (n= 48) or autologous (n = 5).

[g] Patients with acute leukemia (n = 60).

[h] Nodule, ≤29 mm in size.

[i] Mass, ≥30 mm in size.