DR ELENI MAGIRA (Orcid ID : 0000-0002-4430-7886)

DR DIMITRIOS KONTOYIANNIS (Orcid ID : 0000-0002-8051-2940)

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Title: Mixed mold pulmonary infections in hematological cancer patients in a tertiary care cancer center

Authors: Eleni E. Magira[1,2], Ying Jiang[1], Minas Economides[1], Jeffrey Tarrand[3], Dimitrios P. Kontoyiannis[1]

Affiliations:

[1]Department of Infectious Disease, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[2]First Department of Critical Care Medicine, Medical School of National and Kapodistrian University of Athens, Evangelismos Hospital, Athens, Greece

[3]Department of Microbiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

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Corresponding author: Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. Tel.: +1-713-792-6237; fax: +1- 713-745-6839. E-mail address: dkontoyi@mdanderson.org (D.P. Kontoyiannis).

Abstract

There is a paucity of data regarding mixed mold pulmonary infections (MMPIs) in patients with hematologic malignancies **with or without hematopoietic stem cell transplantation (HSCT).** We retrospectively studied 27 such patients (**2005-2015) and compared them to patients with invasive pulmonary aspergillosis (IPA) caused by *Aspergillus fumigatus.* Factors associated with the diagnosis of MMPIs were significant corticosteroid use [20(74%) vs 6(22%), *p*<0.001], sputum as the source specimen [13(48%) vs 3(11%), *p*=0.003], younger age (median age: 58 vs 66 years, *p*=0.006), and male sex [22(81%) vs 13(48%), *p*=0.01]. Hematologic cancers other than acute myeloid leukemia (AML)/myelodysplastic syndromes (MDS) were less common in MMPIs than in IPA patients [AML/MDS: 6(22%) vs 14(52%), *p*=0.04]. Only significant corticosteroid use [95% CI (2.7-42.7), *p*<0.001], and sputum as the source specimen [95% (1.6-41.6), *p*=0.012] were statistically significant as independently associated with increased risk of MMPIs diagnosis in multivariate analysis.** Total mortality rate at day 42 post diagnosis was comparable in both groups.

1 INTRODUCTION

Although invasive pulmonary aspergillosis (IPA) is the predominant mold infection in patients with hematologic cancer, other non-*Aspergillus* molds (e.g. ***Mucorales,*** *Scedosporium spp., Fusarium spp.)* are increasingly reported in such profoundly immunocompromised patients. Although the subject of isolated case reports and small case series (1-8), the occurrence of mixed mold pulmonary infections (MMPIs) has not been studied**.** Specifically, it is unclear patients with poly-fungal pneumonia have more severe disease and worse outcome. To that end, we retrospectively evaluated the incidence, clinical and mycological characteristics, risk factors, and outcome of patients with hematologic cancer who developed MMPIs.

2 PATIENTS AND METHODS

Study design

We retrospectively evaluated all adult (>18 years-old) patients with hematologic malignancy with or without hematopoietic stem cell transplantation (HSCT) who had **proven or probable** pulmonary infection (EORTC/MSG criteria) (9) with >1 mold grown concurrently in sputum or bronchoalveolar lavage (BAL) cultures (e.g., two different species of *Aspergillus* or *Aspergillus spp.* plus non-*Aspergillus spp.*) (cases). **Probable cases based on biomarker detection were not included. As sputum production was often scant in patients with hematologic malignancies, the most common clinical practice in our institution to diagnose microbiologically fungal pneumonia was to proceed with an early (within 72hrs from detection of CT lesions) BAL for culture, cytology and**

galactomannan (serum or/and BAL) detection. For patients, either cases or controls, who were deemed not stable to undergo bronchoscopy attempts to culture sputum was made.

All patients were cared for at MD Anderson Cancer Center from **January 1, 2005 to December 31, 2015**. Detailed epidemiological, clinical, microbiology, treatment, and outcome information were collected from the patients' records based on a standardized case report form**.** Patients with hematologic cancer (from the same time period) with IPA caused by *Aspergillus fumigatus* were used as controls. The study was approved by the MD Anderson Cancer Center Institutional Review Board.

All specimens (sputum, tissue, and BAL) during the study period, were inoculated on two Sabouraud Dextrous Emmons agar plates, one Sabouraud Dextrose Agar tube, and two Brain Heart infusion agar tubes with gentamicin and Mycocel tube media (Becton Dickinson Co. Sparks MD). The media were incubated at 25°C without carbon dioxide for a total of 28 days. Common contaminants in our local outside air such as *Penicillium sp*., *Trichoderma sp*. *Cladosporium sp*. or other dematiaceous molds were reviewed by a pathologist and in the absence of other clinical correlates reported as "contaminant". The method of fungal cultures did not change during the study period. Identification of molds was performed according to established morphologic criteria (10).

Calcofluor WhiteTM stain was performed in the microbiology laboratory. The 15 ml of unspun BAL specimen was first divided according to sample volume requirements for all ordered tests. Calcofluor WhiteTM samples were centrifuged, heat fixed, and directly stained (Alpha Tec Systems, Vancouver, WA). Bronchoscopy was performed using a diagnostic video bronchoscope (Olympus, Tokyo, Japan). After intravenous administration of sedation and routine inspection of the tracheobronchial tree, the bronchoscope was wedged into a segmental or sub-segmental bronchus leading to an area of radiographic concern for infection. Aliquots of 20 ml saline were serially instilled and retrieved until sufficient lavage was recovered for clinically-indicated testing (11). Typically, 80-140 ml was instilled and 35-50 ml was recovered. BAL was aliquoted and 15ml specimens were sent to microbiology, chemistry/hematology and cytopathology.

Definitions

Neutropenia was defined as an absolute neutrophil count (ANC) <500/mm^3 for at least 10 days before the infection. Significant corticosteroid use was defined when a dose of at least 0.3mg/kg/day of prednisone equivalent was administered >21days before MMPIs diagnosis. **A sputum sample had a high probability of being representative of the lower respiratory tract and not from saliva if it contained >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power field**. In sputum from neutropenic patients even when almost no neutrophils were seen, the specimen was judged to be appropriate if the epithelial cell count was less than 25 (12). Clinical criteria (e.g., the

presence of cough, pleuritic chest pain, or purulent/blood tinged sputum), radiological findings (e.g., the presence of pulmonary nodules and/or ground glass and/or cavities and/or consolidation), and the status of the hematologic disease whether on active stage or not were considered to confirm the presence of infection. Malnutrition was defined as a serum albumin level less than 3.0 g/dl. ***Aspergillus*** **galactomannan was measured by using a Platelia *Aspergillus* enzyme immunoassay test kit (Bio-Rad, Hercules, CA) in accordance with the manufacturer's instructions. Serum samples that had an optical density index of ≥0.5 were considered positive and underwent repeated testing to ensure positive results.** Triazole-based treatment indicated a mold-active triazole either alone or in combination with an echinocandin. Liposomal amphotericin-B (L-AmB) based treatment consisted of L-AmB either alone, or in combination with an echinocandin, and/or a mold-active triazole**. Prior exposure to antifungal drugs was defined a 6-months period before the MMPIs diagnosis.** Invasive mold infection (IMI)-attributable mortality was defined as death in a patient with clinical, radiographic, mycological or histological **findings suggestive of active IMI at the time of death.**

Statistical analysis

Descriptive statistics were used to summarize patients data. Incidence densities of MMPIs and all-cause mortality of MMPIs patients at 42 days after the IMI culture were estimated. Categorical variables were compared using Chi-square or Fisher's exact test, as appropriate. Continuous variables were compared using Wilcoxon rank-sum test. Logistic regression analysis was used to identify the factors that were independently associated with mortality. All tests were two-sided tests with a significance level of 0.05. The data analyses were performed using SAS software program (version 9.3; SAS Institute Inc., Cary, NC, USA).

3 RESULTS

Patient characteristics

We identified 27 patients with MMPIs (26 probable, 1 proven) out of 1,156 (2%) patients with hematologic malignancy and fungal pneumonia during the study period. This low incidence density did not change throughout the study period (Figure 1). Table 1 summarizes the demographic characteristics, clinical laboratory data, and antifungal treatment strategies. The median age was 58 years (range, 19-79) and 22 (81%) were males. Nine (33%) patients had acute leukemia (AML in 6), 10 (37%) lymphoma and 8 (30%) other hematologic malignancies. In 2/3 of patients, the hematological cancer was in active stage and 16 (59%) had prior HSCT. A detailed presentation of patients' characteristics with MMPIs is shown in Table 2.

Isolates in the MMPIs group were identified in 48% from sputum, 48% from BAL, and 4% from lung tissue specimen (Table 1). BAL cultures were performed in total 19 and sputum cultures were performed in total 33 in the MMPIs group (n=27). Similarly, in the IPA control group (n=27), BAL cultures were performed in total 26 and sputum cultures were performed in total 24.

The most prevalent identified *Aspergillus* species were *Aspergillus terreus* [11(41%)], followed by *Aspergillus fumigatus* [10(37%)] in the MMPIs group. The most common combination was *Aspergillus fumigatus* plus *Aspergillus terreus* [5(19%)], followed by *Aspergillus terreus* plus *Aspergillus niger* [4(15%)]. *Mucorales spp.* (*Rhizopus, Rhizomucor*, and *Mucor*) as cause of coinfection were in 4 MMPIs cases. Poor outcomes (mortality at day 42 post MMPIs diagnosis) were observed in 7 out of the 10 (70%) MMPIs patients with *Aspergillus spp.* plus non-*Aspergillus spp.* Only 14 patients with MMPIs had serum galactomannan antigen assay, which was positive in 9 (69%) patients (Table 2). Six out of the 9 patients with MMPIs and a positive serum *Aspergillus* galactomannan (67%) were cultured positive for two different species of *Aspergillus,* while 3 patients had *Aspergillus* plus another non-*Aspergillus* mold (e.g. *Rhizopus, Fusarium*). **Direct fungal visualization cytology (BAL and lung tissue specimen) based on direct smear Calcofluor White™ stain was positive in only 4(15%) of MMPIs cases. Three out of the 4 such cases were cultured positive for *Aspergillus* species plus *Mucorales* (Table 2). No BAL specimen was positive by Gomori's methenamine silver nitrate stain.**

Comparison of MMPIs patients with IPA patients due to Aspergillus fumigatus.

There were no significant differences between the control and the MMPIs groups in terms of underlying disease and their treatment, radiologic characteristics, mold-active prophylaxis, and neutropenia, all-cause and attributable mortality at day 42 (Table 1). However, sputum as the specimen source [13(48%) vs 3(11%), p=0.003], and significant corticosteroid use [20(74%) vs 6(22%), p<0.001] was encountered more frequently in the MMPIs group compared to *Aspergillus fumigatus* group. These 2 variables independently associated with MMPIs on both univariate and multivariate analyses [significant use of corticosteroids 95% CI (2.7-42.7), p<0.001, and culture from sputum specimens 95% (1.6-41.6), p=0.012]. **Moreover**, **a sub analysis based only on BAL positive sampling of MMPIs (n=13) vs IPA (n=22) patients (supplementary Table 1) was performed, and found that significant corticosteroid use was the only predisposing factor in the BAL (+) MMPIs patients [9(69%) vs 6(27%), p= 0.015]. In addition males were more likely than females in univariate but not in multivariate analysis to have the diagnosis of MMPIs among the two groups [22(81%) vs 13(48%), p=0.01] (Table 1).**

Regarding antifungal treatment, the heterogeneity of treatment scenarios settings precluded the study from that question. Empiric monotherapy was administered in 19, and combination in 8 of MMPIs patients (Table 2). **Triazole-based or L-AmB based empiric treatments were administered in 18(67%) and 9(34%) respectively in the**

MMPIs group. The type of appropriate empiric treatment (triazole-based vs L-AmB-based) was not associated with 42-day mortality following culture diagnosis of MMPIs.

4 DISCUSSION

Scant data exist regarding MMPIs in immunosuppressed patients as the available literature consists of case reports (1-6), and small case series (7,8). **In a large retrospective Swedish study, coinfection of mucormycosis and aspergillosis was reported at 6% in a subgroup of patients (n=70) with hematologic malignancies (13).** Herein, we describe the largest contemporary series of MMPIs in patients with hematologic cancer. Despite our profoundly immunosuppressed patient population, we found a relatively low incidence rate of such microbiologically documented MMPIs. Although over 1/3 of patients with MMPIs died within 42 days of diagnosis, an outcome that was no statistically different to the one with IPA due to *Aspergillus fumigatus.* Significant corticosteroid use and type of cultured specimen (sputum) were identified as the only factors associated with MMPIs in our case-control comparison. Of note, MMPIs were commonly diagnosed in patients with lymphoid malignancies, typically without them having neutropenia (only in 2 out of 12 lymphoid patients had neutropenia). One explanation could be the broad range immunosuppressive treatment strategies, including corticosteroids that are given in these patients. **Although differences were seen in age and sex distribution between the two groups (younger and more males in the MMPIs patients), this could be an artifact of comparison between small numbers. More research is needed to address age, sex specific patterns and type of opportunistic mold infections.**

The influence of sputum as the source of diagnosis (more cases of MMPIs) might reflect differences in sampling. Alternatively, colonization of the upper airways (sputum as source) by more >1 mold remains a possibility. However, all patients with MMPIs and sputum culture positive results had convincing evidence of mold pneumonia as they were receiving immunosuppression, had compatible clinical and radiological picture and frequent positivity of galactomannan assay. In view of the relatively high positive predictive value (80-90%) of *Aspergillus spp.* sputum positive samples in patients with leukemia (14-16), >1 mold identified from sputum in hematologic patients appears to be a reasonable predictor of a MMPIs in the context of a compatible clinical picture. Importantly, 3 of 9 patients with MMPIs who had positive *Aspergillus* galactomannan in serum, had a non-*Aspergillus* mold growing in addition to *Aspergillus* in sputum or BAL culture. These data, although limited, provide a good example of the fact that high risk patients with hematologic malignancy might have more complex mycobiology as a cause of their pneumonia and *Aspergillus* galactomannan might underestimated that scenario.

Additionally, *Aspergillus terreus* was frequently isolated in patients with MMPIs. *Aspergillus terreus* is a common cause of IPA in our institution (17**), in contrast to most of the other geographic areas.** The comparable survival of patients with MMPIs compared to *Aspergillus fumigatus* controls, could be explained by the widespread **empiric use of**

broad spectrum antifungal therapy. However, as the current mycological diagnostic approaches are suboptimal (18), it is possible that the frequency of MMPIs might be underestimated, in view of low autopsy rates (19). Although MMPIs remains uncommon in our institution, our data might add to the argument that **empiric broad spectrum antifungal therapy** might be justified in institutions with complex epidemiology of IMIs (such is ours), pending further work up and a more specific diagnosis.

Despite its uniqueness, our study had several limitations in view of its retrospective nature and the fact despite it spanned a decade, it had a low number of cases to draw meaningful statistical inferences. Furthermore, our data are drawn from a single center and thus may not be necessarily representative of other hospitals with different epidemiology of fungal pneumonia.

In conclusion, MMPIs remain an uncommon entity in patients with hematological cancer with or without HSCT. MMPIs have comparable mortality to IPA due to *Aspergillus fumigatus*, perhaps because of the prompt **empiric use of broad spectrum** antifungals. Prior significant corticosteroid use is a unique risk factor. Finally, the yield of sputum culture appears high for the diagnosis of MMPIs.

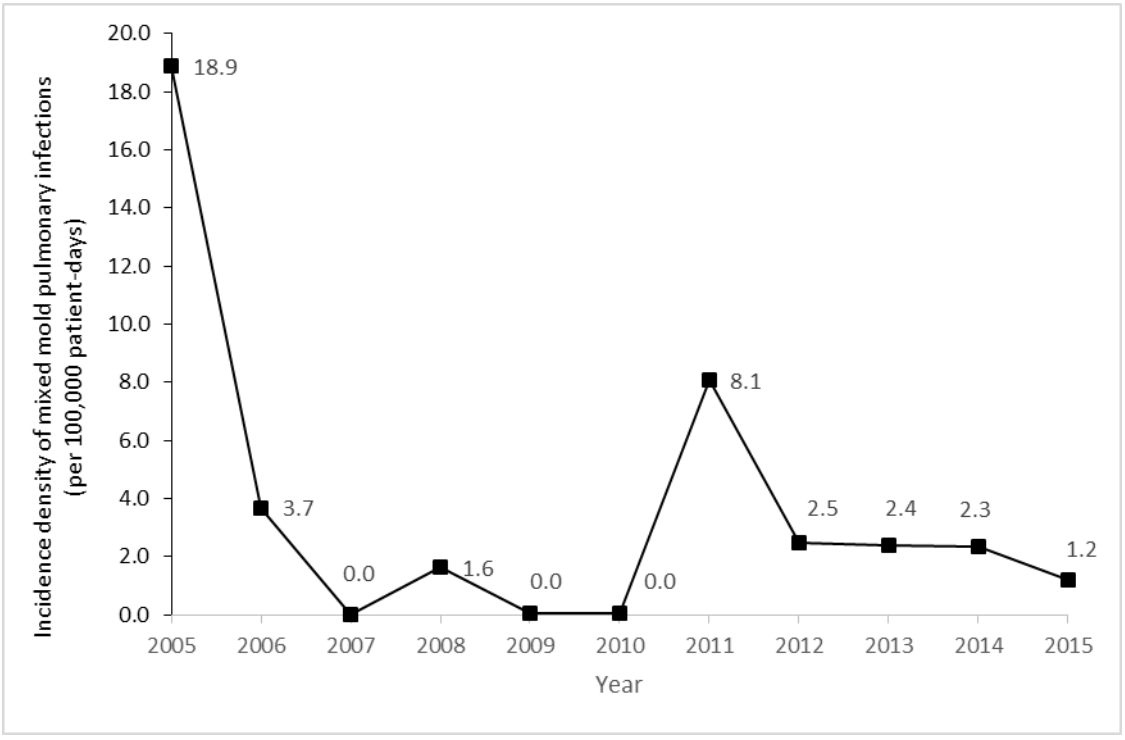

Figure 1. Incidence density (per 100,000 patient-days) of mixed mold pulmonary infections in patients with hematologic cancer or stem cell transplantation between 2005 and 2015

Table 1. Characteristics of patients with mixed mold pulmonary infections (MMPIs) versus patients with invasive pulmonary aspergillus (IPA) due to *Aspergillus fumigatus*

Characteristics	**IPA**	**MMPIs**	***p*-value**[a]
	n=27(%)	**n=27(%)**	
Age, y, median (range)	66 (46-87)	58 (19-79)	0.006
Gender, male	13 (48)	22 (81)	0.01
Race			
White	19 (70)	22 (81)	0.34
Other	8 (30)	5 (18.5)	
Culture specimen			
Sputum	3 (11)	13 (48)	0.003
BAL fluid	22 (81)	13 (48)	0.01
Lung tissue	0 (0)	1 (4)	> .99
Skin soft tissue[b]	2 (7)	4 (15)	0.67
Hematologic malignancy			
AML/ MDS	14(52)	6 (22)	0.04
ALL	1 (4)	3 (11)	0.61
CML	0 (0)	1 (4)	> .99
CLL	5 (19)	5 (19)	> .99
MM	3 (11)	2 (7)	> .99
Lymphoma	4(15)	10 (37)	0.12
History of prior HSCT	10 (37)	16 (59)	0.10
Malignancy status			
Active	19/26 (73)	18 (67)	0.61
Remission	7/26 (27)	9 (33)	
Underlying medical condition			
Diabetes mellitus	6 (22)	5 (19)	0.74
Chronic lung disease (COPD)	6 (22)	4 (15)	0.48
Laboratory findings at diagnosis	13/26 (50)	10 (37)	0.34

Neutropenia (ANC<500 cells/µL)			
Lymphopenia (ALC<500 cells/µL)	14/26 (54)	14 (52)	0.88
Albumin (<3.0 g/dL)	15/26 (58)	18 (63)	0.69
History of immunosuppressant[c]			
Calcineurin inhibitors[d]	6 (22)	10 (37)	0.23
Monoclonal antibodies[e]	6 (22)	9 (33)	0.36
Nucleoside analogues[f]	7 (26)	8 (30)	0.76
Significant corticosteroid use[g]	6 (22)	20 (74)	< .001
Cavitation in radiology	4 (15)	3 (11)	> .99
Prior exposure to mold-active azoles	7 (26)	8 (30)	1.00
Total duration (days), median (IQR)	66 (14-175)	117 (58-171)	0.64
Outcome at 42 days			
All-cause mortality	9 (33)	11 (41)	0.57
Death attributable to IMI	6 (22)	10 (37)	0.23

Data are presented as No. (%).

Abbreviations: ALC, absolute lymphocyte count; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; BAL, bronchoalveolar lavage; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; COPD, chronic obstructive pulmonary disease; HSCT, hematopoietic stem cell transplantation; IMI, invasive mold infection; IQR, interquartile range; L-AmB, liposomal amphotericin B; MDS, myelodysplastic syndrome; MM, multiple myeloma;

[a]*p* values of tests comparing IPA due to *Aspergillus fumigatus* vs MMPIs

[b]Site of primary infection that cultured positive either alone (in IPA patients) or in addition to other specimens (in MMPIs patients)

[c]Drugs used within 12 weeks of culture date.

[d]Calcineurin inhibitors included cyclosporine and tacrolimus.

[e]Monoclonal antibodies included tumor necrosis factor α blockers, alemtuzumab, and other cytotoxic monoclonals.

[f]Nucleoside analogues included cytarabine, fluorouracil, gemcitabine, and methotrexate.

[g] Administration of corticosteroids (0.3 mg/kg/day of prednisone equivalent) >21days before MMPIs diagnosis

Table 2. Infection characteristics of 27 patients with mixed mold pulmonary infections (MMPIs)

CASES	Diagnosis	Age Gender	Status	ANC	Specimen	Cortico-steroids	sGM index	Direct microscopy	Chest CT	Prophy-laxis	Fungus coinfection	Empiric antifungal therapy	Mortality day 42
1	AML	**71 M**	A	N	BAL	<600	0.1	**hyphae**	GG	NONE	*Asp fumigatus + Rhizomucor*	L-AmB	Y
2	ALL	**19 F**	A	Y	BAL	N	1.78/9.52	**hyphae**	ATEL	FLU	*Asp non-fumigatus + Rhizopus*	VRC	Y
3	AML	**40 M**	A	N	BAL	>600	NP	**negative**	CONS	CSP	*Asp terreus + Scedosporium spp.*	L-AmB+VRC	Y
4	ALL	**33 M**	A	N	BAL	N	NP	**negative**	ND	ITR	*Asp niger + Paecilomyces spp.*	VRC	N
5	CLL	**62 M**	A	Y	BAL	<600	NP	**negative**	GG ND	ITR	*Asp fumigatus + Asp non-fumigatus*	L-AmB+VRC+CSP	Y
6	CLL	**79 M**	A	Y	BAL	<600	NP	**negative**	GG	FLU	*Asp terreus + Asp flavus*	L-AmB+VRC+CSP	Y
7	CLL	**65 M**	A	N	BAL	N	0.17	**negative**	CONS	NONE	*Asp niger + Asp non-fumigatus*	L-AmB	N
8	CLL	**67 F**	A	N	BAL	N	NP	**negative**	GG ND	NONE	*Asp terreus + Asp flavus*	VRC	N
9	AML	**72 M**	A	Y	SPUT	N	0.67	**negative**	GG	FLU	*Asp terreus + Asp non-fumigatus*	VRC+CSP	Y
10	AML	**65 M**	R	N	SPUT	N	NP	**negative**	ND	CSP	*Asp niger + Asp flavus*	VRC+CSP	N
11	AML	**31 M**	A	N	SPUT	>600	0.77/0.95/0.97	**negative**	CAV	FLU	*Asp fumigatus +Asp non-fumigatus*	L-AmB	Y
12	CLL	**77 M**	A	N	SPUT	N	0.83/0.77	**negative**	GG ND	NONE	*Asp fumigatus + Asp non-fumigatus*	L-AmB+CSP	N
13	CML	**49 M**	A	N	SPUT	<600	NP	**negative**	CONS	PCZ	*Asp fumigatus + Asp terreus*	PCZ	N
14	AML	**49 M**	A	N	BAL	<600	0.57/0.53/8.2	**negative**	GG	FLU	*Asp fumigatus + Asp terreus + Asp niger*	L-AmB+VRC	N
15	ALL	**61 M**	A	N	TIS	<600	3.5	**hyphae**	GG ND	FLU	*Asp flavus + Fusarium spp.*	VRC	Y
16	HL	**60 M**	A	Y	BAL	<600	NP	**hyphae**	GG ND	FLU	*Asp fumigatus + Mucor*	L-AmB+CSP	Y
17	NHL	**31 M**	R	N	BAL	<600	NP	**negative**	GG ND	NONE	*Asp vecicolor + Paecilomyces spp.*	PCZ	N
18	NHL	**57 M**	A	N	BAL	<600	0.178	**negative**	CONS	FLU	*Asp niger + Asp flavus*	VRC	N
19	NHL	**44 M**	R	N	SPUT	<600	NP	**negative**	GG ND	FLU	*Asp fumigatus + Asp terreus*	VRC	N
20	NHL	**58 M**	R	Y	SPUT	<600	NP	**negative**	EFF	VRC	*Asp niger + Fusarium spp.*	VRC	Y
21	NHL	**38 M**	R	N	SPUT	>600	NP	**negative**	CAV	PCZ	*Asp fumigatus + Scedosporium spp.*	VRC	N
22	NHL	**51 F**	A	N	SPUT	>600	0.09/0.0	**negative**	GG ND	FLU, VRC	*Asp fumigatus + Asp terreus*	VRC	N
23	MM	**64 M**	A	N	SPUT	>600	0.15	**negative**	ND	FLU	*Asp flavus + Asp non-fumigatus*	VRC	N
24	MM	**69 M**	R	N	SPUT	>600	0.6/0.73	**negative**	CONS	FLU	*Asp niger + Asp terreus*	VRC	N
25	HL	**57 M**	A	N	SPUT	>600	NP	**negative**	CONS	PCZ	*Asp niger + Asp terreus*	PCZ	N
26	HL	**30 F**	A	N	SPUT	<600	7.6/7.5	**negative**	CAV ND	VRC	*Asp glaucus + Rhizopus*	PCZ	Y
27	NHL	**66 F**	R	N	BAL	<600	0.73	**negative**	GG	FLU	*Asp niger + Asp terreus + Asp flavus*	VRC	N

Abbreviations:

A, active stage of disease; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; ATL, atelectasis; BAL, bronchoalveolar lavage; CAV, cavity; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CSP, caspofungin; CON, consolidation; F, female; FLU, fluconazole; GG, ground glass; sGM, serum galactomannan; HL, Hodgkins lymphoma; HSCT, hematopoietic stem cell transplantation; ITC, itraconazole; L-AmB, liposomal amphotericin B; M, male; MM, multiple myeloma; N, no; ND, nodules; NHL, non-Hodgkins lymphoma; NP, not performed; PCZ, posaconazole; R, in remission; SPUT, sputum; spp., species; VRC, voriconazole; Y, yes;

DISCLOSURES

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CONFLICT OF INTERSTS

None relevant to this study

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REFERENCES

1. Mölle M, Blaschke-Hellmessen R, Schuler U, Nowak R, Ehninger G. Disseminated aspergillosis and mucormycosis. **A case report.** *Mycoses*. 1996;39:59-64.

2. McLintock LA, Gibson BE, Jones BL. *Mixed pulmonary fungal infection with Aspergillus fumigatus* and *Absidia corymbifera* in a patient with relapsed acute myeloid leukaemia. *Br J Haematol*. 2005;128:737.

3. Davoudi S, Anderlini P, Fuller GN, Kontoyiannis DP. A long-term survivor of disseminated Aspergillus and mucorales infection: an instructive case. *Mycopathologia*. 2014;178:465-470.

4. Lopes JO, de Mello ES, Klock C. Mixed intranasal infection caused by *Fusarium solani* and a zygomycete in a leukaemic patient. *Mycoses*. 1995;38:281-284.

5. Vasiloudes P, Morelli JG, Weston WL. Painful skin papules caused by concomitant Acremonium and Fusarium infection in a neutropenic child. *J Am Acad Dermatol.* 1997;37:1006-1008.

6. **Bergantim R, Rios E, Trigo F, Guimarães JE. Invasive coinfection with Aspergillus and Mucor in a patient with acute myeloid leukemia. *Clin Drug Investig*. 2013;33 Suppl 1:S51-55.**

7. Georgiadou SP, Kontoyiannis DP. Concurrent lung infections in patients with hematological malignancies and invasive pulmonary aspergillosis: how firm is the Aspergillus diagnosis? *J Infec* 2012 ;65:262-268.

8. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis.* 2002; 34:909–917.

9. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008;46:1813–1821.

10. **Brandt ME, Warnock DW. Taxonomy and Classification of Fungi. In Jorgensen JH, ed. *Manual of clinical microbiology*. 11th ed. Washington, DC: AMS Press; 2011:1935 – 1943.**

11. **Sampsonas F, Kontoyiannis DP, Dickey BF, Evans SE. Performance of a standardized bronchoalveolar lavage protocol in a comprehensive cancer center: a prospective 2-year study. *Cancer*. 2011;117:3424-3433.**

12. Geckler RW, Gremillion DH, McAllister CK, Ellenbogen C. Microscopic and bacteriological comparison of paired sputa and transtracheal aspirates. *J Clin Microbiol*. 1977;6:366–369.

13. **Klingspor L, Saaedi B, Ljungman P, Szakos A. Epidemiology and outcomes of patients with invasive mould infections: a retrospective observational study from a single centre (2005–2009). *Mycoses*. 2015;58(8):470-477.**

14. Yu VL, Muder RR, Poorsattar A. Significance of isolation of Aspergillus from the respiratory tract in diagnosis of invasive pulmonary aspergillosis: results from a three-year prospective study. *Am J Med*. 1986;81:249e54.

15. Nalesnik MA, Myerowitz RL, Jenkins R, Lenkey J, Herbert D. Significance of Aspergillus species isolated from respiratory secretions in the diagnosis of invasive pulmonary aspergillosis. *J Clin Microbiol*. 1980;11:370e6.

16. Horvath JA, Dummer S. The use of respiratory-tract cultures in the diagnosis of invasive pulmonary aspergillosis. *Am J Med* 1996;100:171e8.

17. **Hachem RY, Kontoyiannis DP, Boktour MR, et al. *Aspergillus terreus*: an emerging amphotericin B-resistant opportunistic mold in patients with hematologic malignancies. *Cancer*. 2004;101:1594-1600.**

18. Ambasta A, Carson J, Church DL. The use of biomarkers and molecular methods for the earlier diagnosis of invasive aspergillosis in immunocompromised patients. *Med Mycol.* 2015;53(6):531-557.

19. Lewis RE, Cahyame-Zuniga L, Leventakos K, et al. Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study. *Mycoses.* 2013;56(6):638-645.