





Dematiaceous fungal infection in solid organ transplantation

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• There is no conflict of interest to declare. Presented at Mileaker. Presented at Speaker.





Dematiaceous Fungi (black fungi)

- A large and heterogenous group of filamentous molds;
- With dark colored colonies and cell walls;
- Produce brown melanin or melanin-like pigment in the cell wall of their hyphae or conidia, or both;



Pathogenic dematiaceous fungi and taxonomy

Ascomycota

Chaetothyriales

-Cladophialophora、Exophiala、Fonsecaea、 Ochroconis、Phialophora and Rhinocladiella

• Dothideales

—Aureobasidium and Hormonema)

Sordariales

— Phaeoacremonium, Chaetomium) and Madurella

- Pleosporales
 - —Alternaria, Bipolaris, Curvularia and Exserohilum



Austomycosis Phaeohyphomycosis * Eumycotic mycetoma * Onychomycosis * Tinea nigra * Black piedra * Keratitis **Clinical diseases**

Phaeohyphomycosis in China

- 174 cases of proven phaeohyphomycosis reported in Chinese and English literature from 1987 to 2021 were reviewed according to the classification definitions;
- Epidemiology, species of dematiaceous fungi, MIC values, clinical features, treatments, and prognosis were analyzed;
- The most common risk factors were traumas (37%), diabetes (11%), and corticosteroid use (11%); CARD9 deficiency (7%), kidney transplantations (3%), were frequent risk factors in patients with disseminated, CNS, deep local, and pulmonary infections;
- The mortality of cerebral, disseminated and pulmonary phaeohyphomycosis are 55%, 36%, and 25%;
- The overall misdiagnosis rate of phaeohyphomycosis was 74%. Moderate to severe rashes are accounting for 82% of subcutaneous phaeohyphomycosis.;



Number of the cases since 1987 to 2021





Demographics & risk factors of phaeohyphomycosis

TABLE 1 Demographics and risk	c factors of phaec	hyphomycosis	in China.			<u></u>	*	
Infection type	Total	CNS	Disseminated	Pulmonary	Deep- local	Subcutaneous	Keratitis	Superficial
Demographics (Ratio %)	n=174	n=11	n=11	D=8 S	n=10	1=85	n=26	n=23
Male	107 (61%)	11 (100%)	5 (45%)	V (88%)	6 16095	49 (58%)	16 (62%)	13 (57%)
Female	67 (39%)	0 (100%)	6 (55%)	1 (13%)	4 (40%)	36 (42%)	10 (38%)	10 (43%)
Age, mean (year)	48	29	26	54	61	51	57	37
Range (year)	2-89	4-73	9-56	10-89	45-75	2-89	22-79	2-87
Risk factor (Ratio %)	2	96	0.81					
Stem cell transplantation	- 010%i	0-10%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Heart transplantation	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Lung transplantation	0.(0%5)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Liver transplantation	2(1%)	0 (0%)	0 (0%)	1 (13%)	1 (10%)	O (O%)	0 (0%)	0 (0%)
Kidney transplantation	5 (3%)	0 (0%)	1 (9%)	1 (13%)	0 (0%)	3 (4%)	0 (0%)	0 (0%)
Graft vs host disease	1 (1%)	0 (0%)	1 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Corticosteroid use	20 (11%)	0 (0%)	1 (9%)	1 (13%)	1 (10%)	14 (16%)	0 (0%)	3 (13%)

He Y., et al. Frontiers in Cellular and Infection Microbiology, 2022



Demographics & risk factors of phaeohyphomycosis

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TABLE 1 | Continued

Infection type	Total	CNS	Disseminated	Pulmonary	Deep- local	Subcutaneous	Keratitis	Superficial
Other immunosuppressants	9 (5%)	0 (0%)	0 (0%)	1 (13%)	1 (10%)	5 (6%)	0 (0%)	2 (9%)
Malignancy	9 (5%)	1 (9%)	1 (9%)	0 (0%)	2 (20%)	4 (5%)	1 (4%)	0 (0%)
Chemotherapy	3 (2%)	0 (0%)	1 (9%)	0.(0%)	1 (10%)	(0%)	1 (4%)	0 (0%)
Neutropenia	2 (1%)	0 (0%)	0 (0%)	1 (13%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)
HIV/AIDS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Primary T-cell	1 (1%)	0 (0%)	0 (0%)	Q (Q%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
immunodeficiency		10						
CARD9 mutation	12 (7%)	1 (9%)	2 (18%)	0 (0%)	0 (0%)	9 (11%)	0 (0%)	0 (0%)
Malnutrition	10 (6%)	0 (0%)	2 (18%)	1 (13%)	1 (10%)	6 (7%)	0 (0%)	0 (0%)
Pregnancy	3 (2%)	0 (0%)	(9%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Trauma	65 (37%)	2 (18%)	5 (45%)	0 (0%)	4 (40%)	25 (29%)	22 (85%)	7 (30%)
Smoke	2 (1%)	0 (0%)	1 (9%)	1 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diabetes mellitus	20 (11%)	2 (18%)	1 (9%)	0 (0%)	4 (40%)	12 (14%)	0 (0%)	1 (4%)
Chronic liver disease	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (4%)	0 (0%)
Chronic pulmonary disease	11 (69%)	0 (0%)	1 (9%)	2 (25%)	0 (0%)	8 (9%)	0 (0%)	0 (0%)
Chronic renal disease	4 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	3 (3%)	0 (0%)	0 (0%)
Chronic heart disease	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (3%)	0 (0%)	0 (0%)
No risk factor	38 (22%)	3 (27%)	0 (0%)	2 (25%)	1 (10%)	19 (22%)	2 (8%)	11 (48%)

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Solid organ transplantation

- Solid organ transplantation (SOT) is an established and practical definitive treatment option for patients with end-organ dysfunction;
- The evolution of SOT has seen the field progress rapidly over the past few decades with incorporation of a variety of solid organs—liver, kidney, pancreas, heart, and lung—into the donor pool;
- The SOT recipients are particularly at risk of invasive infections due to prolonged immunosuppression



Phaeohyphomycosis & pathogens

Different clinical types



STI) Disseminated

Cutaneous (SSTI)

ed Pulmanary

CNS



A variety of pathogens

Guidelines of AST-IDCOP

Received: 29 January 2019 Accepted: 27 February 2019

DOI: 10.1111/ctr.13525

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Emerging fungal infections in solid organ transplant recipients: Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice

Shmuel Shoham¹ | Edward A. Dominguez² | on behalf of the AST Infectious Diseases Community of Practice

Hsoham S. et al, Clinical Transplantation. 2019;33:e13525.



Review from 1973~2022

REVIEW

Dematiaceous fungal infections in solid organ transplantation: Systematic review and Bayesian meta-analysis

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Abstract

Andrew J. Radcliffe²

Background: Dematiaceous fungi cause a number of infectious syndromes referred to as phaeohyphomycosis among both immunocompetent and immunocompromised hosts. We performed a systematic review to characterize these infections in solid organ transplant recipients (SOTR).

Marwan M. Azar

TRANSPLAN INFECTIOUS Disease

Methods: We searched PubMed database (last searched 1/6/2022) for Englishlanguage reports on dematiaceous fungal infections in SOTR. Included reports needed individualized demographic, treatment, and outcome data; pediatric reports were excluded. A universally applicable bias assessment was performed on reports. Models



Case series & literature review



Review

Phaeohyphomycosis in Solid Organ Transplant Recipients: A Case Series and Narrative Review of the Literature

Davide Lo Porto ^{1,*}, Andrea Cona ¹, Francesca Todaro ¹, Elena De Carolis ², Francesca Cardinale ¹, Neha Hafeez ³, Giuseppina Di Martino ¹, Pier Giulio Conaldi ¹, Maurizio Sanguinetti ², Paolo Antonio Grossi ⁴, and Alessandra Mularoni ¹



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Lo Proto D, et al. J. Fungi 2023, 9, 283.https://doi.org/10.3390/jof9030283



Presented at speak 2. Infection types 3. Microbiology and risk factors 4. The

- Microbiology and susceptibility results



Epidemiology and risk factors

- A total of 149 reports on 201 cases of dematiaceous fungal infections in SOT recipients published between 1973 and 2022. (94 cases published between 2011 and 2022)
- All transplant patients are at risk and infections can occur at all times along the post-transplant continuum.

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62040	Total (n = 201)
Age (mean ± SD)	54 ± 12
Male (No., %)	144 (72%)
Transplant Organ	
Kidney	122 (61%)
Lung	25 (12%)
Heart	26 (13%)
Liver	8 (4%)
Pancreas or combination	
Time between transplant and infection (months, mean ± SD)	31 ± 42

NETWORK

Epidemiology and risk factors

- Development of infection requires that a susceptible host comes in contact with the causative fungus and that the fungus survives and thrives within the patient.
- Exposure to emerging fungi is generally due to direct cutaneous contact from the environment sources.

Reported exposuregardening35trauma21



Infection types

• Skin and soft tissue infection (SSTI) was the most common infection type (73%), followed by CNS (11%) and disseminated (11%) infections.

AU90 ri	Total (n = 201)
Transplant Organ	9
SSTI (No.), at Nie aker	146 (73%)
central nervous system (CNS) infection (No.)	22 (11%)
Disseminated infection (No.)	22 (11%)
Pulmonary infection (No.)	11 (5%)



Infection types





CNS infection

Pulmonary infection

(a)



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Alternaria alternata

Exophiala xenobiotica

Verruconis gallopava



Microbiology and susceptibility

• Minimum inhibitory concentration (MIC) values derived from BMD methods or Sensititre YeastOne (Thermo Fisher Scientific) were available for 37/58 (64%) fungal isolates.

Genus	Species	Amphotericin Β (μg/ml)	Ketoconazole (µg/ml)	Fluconazole (µg/ml)	ltraconazole (µg/ml)	Voriconazole (µg/ml)	Posaconazole (µg/ml)	lsavuconazole (µg/ml)	Anidulafungin (µg/ml)	Caspofungin (µg/ml)	Micafungin (µg/ml)	Flucytosine (µg/ml)	Terbinafine (μg/ml)
Acrophialophora	Acrophialophora levis			8	0.06	0.25	0.06	0.25	^{0.5}	1	1		
Alternaria	Alternaria spp.	0.04-1.0	0.78	2-32	0.03-1.0	1-4	0.125-0.25	in		<0.03-1.0			
	Alternaria alternata	0.25-1.0		32-256	0.5-4	0.125-0.25	0.125-0.25	(19)	0.125	0.25	0.06		
	Alternaria anthropophila	2		11 -	0.125	1	0.125	*	0.5 ^{MEC}	0.5 ^{MEC}	0.125 ^{MEC}		0.5
	Alternaria infectoria	2	+	>64	0.5	4				4 ^{MEC}		>64	8
Cladophialophora	Cladophialophora bantiana	<0.5	7 3,	-0	esi	0.5	0.016	0.25	0.031				
Colletotrichum	Colletotrichum crassipes	hie	8	>16	2	2						>128	2
Exophiala	Exophiala dermatitidis	1	nt U	4.0	0.5	0.032	0.125	0.125	>16				
	Exophiala spinifera	≤0.14	0.2		≤0.018							≤10.09	
	Exophiala xenobiotica	16	1		16	2	0.125						>0.5



Microbiology and susceptibility

Genus	Species	Amphotericin B (µg/ml)	Ketoconazole (µg/ml)	Fluconazole (µg/ml)	ltraconazole (µg/ml)	Voriconazole (µg/ml)	Posaconazole (µg/ml)	lsavuconazole (µg/ml)	Anidulafungin (µg/ml)	Caspofungin (µg/ml)	Micafungin F (μg/ml)	Flucytosine µg/ml)	Terbinafine (µg/ml)
Cladophialophora	Cladophialophora bantiana	<0.5				0.5	0.016	0.25	0.031	$\cdot \gamma$	320		2.
Colletotrichum	Colletotrichum crassipes	1	8	>16	2	2			1	5	oľ	128	2
Exophiala	Exophiala dermatitidis	1		4.0	0.5	0.032	0.125	0.125	>16	re	Ser		
	Exophiala spinifera	≤0.14	0.2		≤0.018		10	U S	+6		4	≤10.09	
	Exophiala xenobiotica	16	1		16	2	0.125		JUr.				>0.5
Medicopsis	Medicopsis romeroi	0.25-8.0			8 to > 16	0.5-2.0	0.5-2.0		9	1 to > 16			0.25 to > 16
Microsphaeropsis	Microsphaeropsis arundinis	0.5-1.0	\$. N	<0.015- 0.032	0.06	<0.008						
Paraconiothyrium	Paraconiothyrium cyclothyrioides	0.25	23		0.125	0.25	0.03						
Phaeoacremonium	Phaeoacremonium parasiticum	0.25-8		5 S	0.03-2	0.03-0.25	0.03-0.125						
Phomopsis	Phomopsis longicolla	0.03	+ ()	0.25	0.015	0.015			≤0.03			1
Pleurostoma	Pleurostoma richardsiae	0.5	nr.	128	1	2	1		>8	>8	>8 >	>64	
Rhinocladiella	Rhinocladiella mackenziei	≤0.03			≤0.015		≤0.015				٤	3	
Scopulariopsis	Scopulariopsis brumptii	0.8		780	0.07								
Veronaea	Veronaea botryosa			>64	0.25	2							
Verruconis	Verruconis gallopava	<0.12-1.0	0.8	20-128	0.06-0.25	0.13-1.0	0.06-0.125		0.06	0.25	0.03 2	2-128	

DICAL MYCOLOGY

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MICs of different antifungals against 52 isolates of *B.spicifera* (mg/L)

Antifungals	GM	MIC Range	MIC ₉₀	2
ANI	0.06	<0.015->8	0.25	
AMB	0.21	<0.03-2	gus 1 hts	
CAS	0.89	-0.25-2	II rigi	
ITC	0.63	<0.03-4	1	
FLU	38.7	4->64	>64	
FC	ent >64, of	>64	>64	
MIK	0.05	<0.015-0.125	0.125	
POSCO	0.26	<0.03-1	0.5	
VRC	1.56	0.25-4	2	



da Cunha KC, et al. J Clin Microbiol. 2012.

MICs of different antifungals against 37 isolates of *C. bantiana* (mg/L)

Antifungals	GM	MIC Range	MIC ₅₀) •
АМВ	0.7	0.125-2	1	-6 1 SEK	16
FLU	35.14	16-64	32 5	64	
ITC	0.064	<0.016-0.25	0.063	0.125	
VRC	0.769	0.125-4	r. Palling	2	
POS	0.044	<0.016-0.25	0.031	0.125	
ASV	e ^{0.259} 0	S 0.008-1	0.25	0.5	
CAS	2.551	1-8	2	4	
	0.073	0.016-4	0.063	2	

Badali H, et al. J Clin Microbiol, 2010

C



MICs of different antifungals against 11 isolates of *Ochroconis musae* (mg/L)

Antifungals	GM	MIC Range		.3.
AMB	28.36	8-32	1 1 320	erve
ІТС	7.00	1-32	51 32 165	
POS	18.23	0.5-32	righ32	
VRC	11.09	2-32	32	
ANI	3.93 at	0.015-32	4	
CAS	te 7.90 f S	1-32	4	
MIKCES	0.22	0.06-0.5	0.25	
TERB	0.03	0.015-0.025	0.02	





MICs of different antifungals against 18 isolates of *Verruconis gallopava* (mg/L)

Antifungals	MIC Range	MIC ₅₀	MIC ₉₀	GM 2)LJ.
AMB	0.125-4	0.25	0.5	A 0.54	serve
FC	0.5-64	4	AUS	11.53	
FLU	4->64	64	>64	52.22	
ITC	0.016-4	0.125	er .0.5	0.40	
VRC	0.5-2	f spear	2	1.06	
POSES	<0.016-4	0.031	0.125	0.28	
CAS	0.25-1	0.5	1	0.64	
ANI	0.016-0.125	0.031	0.063	0.04	
					C

Seyedmousavi S, et al. Antimicrob Agents Chemother, 2014



MICs of different antifungals against 43 isolates of *E. dermatitidis* (mg/L)

Antifungals	MIC Range	GM		
АМВ	0.12-2	1.19	NUQUIST	S res2
FC	0.12-64	0.24	Alliright	4
VRC	0.015-1	0.06 ake	0.06	0.25
itc Dre	Se ^{0.015-1}	5 0.05	0.06	0.25
TERB	0.015-0.25	0.02	0.015	0.03

Duarte AP, et al. Mycopathologia, 2013



Therapy and outcome

• The median duration of therapy was 5 months (range 0.1–40 months) for the 120 cases which reported treatment duration, reflecting the heterogeneity of presentations and clinical courses across the reports. Present of St COPY

	10 fotal (n = 201)
Duration of therapy (months, mean [range])	5 [0.1-40]
Choose of antifungal agents	
→ Itraconazole	91 (45%)
Voriconazole	59 (29%)
> Posaconazole	18 (9%)
Isavuconazole	3 (1%)
Amphotericin B	57 (28%)
Receipt of ≥2 antifungal agents (No., %)	65 (32%)
Disseminated infections (No., %)	47 (73%)
Without antifungal therapy (No., %)	23 (11%)
SSTIs (No., %)	22 (96%)
	MEDICAL MYCO

Therapy and outcome











Case 1



- A renal transplant recipient with a cutaneous phaeohyphomycosis due to Alternaria species
- Clinical improvement was achieved by combination of amphotericin B wet-packing and systemic antifungal therapy with oral voriconazole

Hsu C.C., et al. Asian Journal of Surgery (2015) 38, 47e57



Case 2



- A renal transplant recipient with subcutaneous phaeohyphomycosis due to *Hongkongmyces* snookiorum.
- The condition improved significantly by systemic antifungal therapy with oral voriconazole



Case 3



Chest radiographs before admission (A) and upon admission (B)

 A case of *Lasiodiplodia theobromae* pneumonia in a patient who died 14 days after cadaveric-liver transplantation. A dematiaceous mold was recovered and identified as *L. theobromae* by microscopic morphology and EF1 gene sequencing.



Phaeohyphomycosis in China

- 174 cases of proven phaeohyphomycosis reported in Chinese and English literature from 1987 to 2021 were reviewed according to the classification definitions;
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Number of the cases since 1987 to 2021





Demographics & risk factors of phaeohyphomycosis

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Risk factor (Ratio %)	2	24	0.81					
Stem cell transplantation	- 010%f	0-10%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Heart transplantation	1 (1%).	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Lung transplantation	0.(0%5)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
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He Y., et al. Frontiers in Cellular and Infection Microbiology, 2022



Demographics & risk factors of phaeohyphomycosis

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TABLE 1 | Continued

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Chemotherapy	3 (2%)	0 (0%)	1 (9%)	0.(0%)	1 (10%)	(0%)	1 (4%)	0 (0%)
Neutropenia	2 (1%)	0 (0%)	0 (0%)	1 (13%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)
HIV/AIDS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Primary T-cell	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
immunodeficiency		10						
CARD9 mutation	12 (7%)	1 (9%)	2 (18%)	0 (0%)	0 (0%)	9 (11%)	0 (0%)	0 (0%)
Malnutrition	10 (6%)	0 (0%)	2 (18%)	1 (13%)	1 (10%)	6 (7%)	0 (0%)	0 (0%)
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Chronic liver disease	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (4%)	0 (0%)
Chronic pulmonary disease	11 (69%)	0 (0%)	1 (9%)	2 (25%)	0 (0%)	8 (9%)	0 (0%)	0 (0%)
Chronic renal disease	4 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	3 (3%)	0 (0%)	0 (0%)
Chronic heart disease	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (3%)	0 (0%)	0 (0%)
No risk factor	38 (22%)	3 (27%)	0 (0%)	2 (25%)	1 (10%)	19 (22%)	2 (8%)	11 (48%)





Summary

- Dematiaceous fungi are important causes of infection in SOT recipients.
- An early diagnosis and therapy are critical in preventing the dissemination of disease.
- The diagnosis relies on clinical suspicion paired with mycological investigation.
- Treatment of these infections continues to be a challenge.

As cases increase, further studies are becoming necessary to determine the optimal management strategy in this vulnerable immunosuppressed population.



Thanks for your attention!



国家皮肤与免疫疾病临床医学研究中心 ォ etional Clinical Research Center for Skin and Instance Discusses ※まえずまーまえ Poking University First Maspital

সামাম