



## How do I *manage* systemic phaeohyphomycosis?

**Professor Ruoyu Li**

Professor, Department of Dermatology  
Peking University First Hospital  
Peking University Research Center for Medical Mycology  
Beijing, China



MMTN Malaysia Conference 2019  
20-21 July 2019 • G Hotel Gurney, Penang, Malaysia



## Systemic Phaeohyphomycosis -management

Ruoyu Li, MD.

National Clinical Research Center for Skin and Immune Diseases  
Dept. Dermatology, Peking University First Hospital,  
Research Center for Medical Mycology,  
Peking University, Beijing, China



Supported by:

## Conflict of Interest

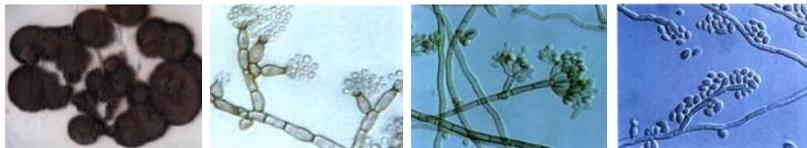
Ruoyu Li has participated in advisory boards and/or as investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Bayer, Janssen-Cilag, MSD and Pfizer Inc.

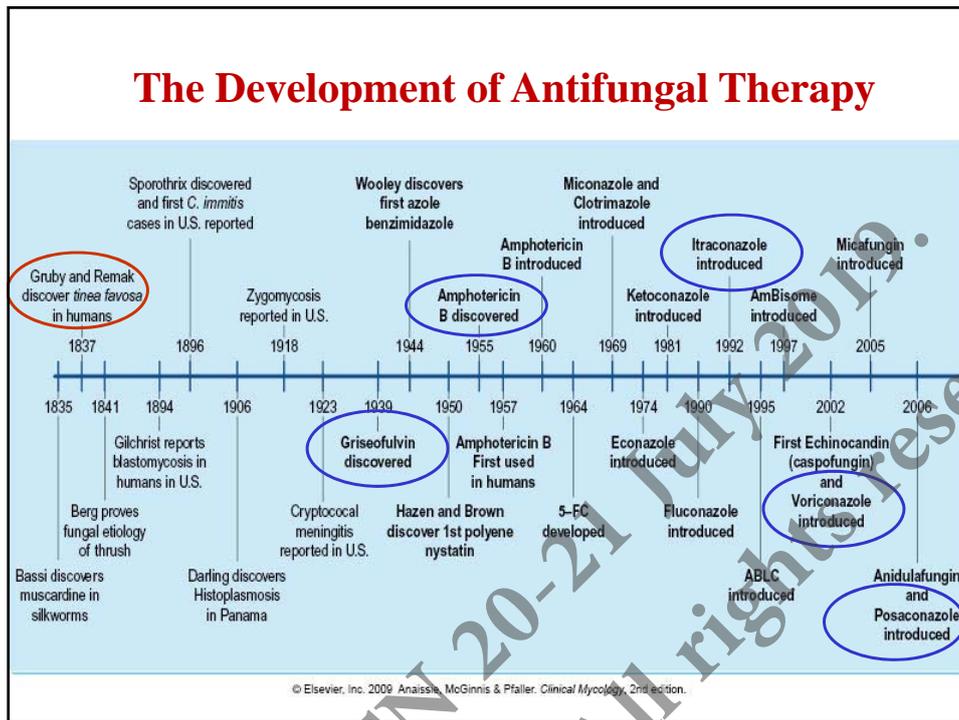
## Phaeohyphomycosis & pathogens

### Different clinical types



### A variety of pathogens





**No standard approach  
for treatment of  
phaeohyphomycosis**

## **ESCMID & ECMM joint clinical guidelines for the diagnosis & management of systemic phaeohyphomycosis**

- VOR, POS and ITC are the most consistent *in vitro* activity
- Oral ITC given extensive clinical experience
- VOR may be superior for CNS infections
- POS is a well-tolerated alternative drug, with excellent salvage treatment results
- **Combination antifungal therapy** is recommended for cerebral abscesses, and disseminated infections

Chowdhary A, et al., Clin Microbiol Infect, 2014

## **Recommendations for treatment-I**

- **Localized cutaneous infection or subcutaneous nodule (s):** Surgery (AII)
- **Subcutaneous nodules:** Cryotherapy, laser, heat, or KI (BIII)
- To prevent dissemination: ITC or VRC 400mg (BIII)
- **Multiple subcutaneous nodules:** ITC 400mg or VRC 400mg (AIII), ITC 200mg, POS 800mg, AMB 1mg/kg, Liposomal AMB (3mg/kg), CAS (70/50mg), TERB 250~500mg (CIII)
- Combination: ITC+TERB or ITC+AMB (CIII)**

Chowdhary A, et al., Clin Microbiol Infect, 2014

## Recommendations for treatment-II

- **Pulmonary infection:** Liposomal AMB (3mg/kg), ITC 400mg, VRC 400mg, POS 800mg (BIII)
- **Solitary nodule in immunocompetent:** Surgery(BIII)
- **Sinus fungus ball:** Surgery (AII)
- **Invasive sinusitis:** Liposomal AMB 2w followed by VRC 3m (CIII)
- **Cerebral abscess:** complete excision (AII), VRC 400mg, POS 800mg (CII), AMB (DIII)
- New combinations: VRC or POS plus ECHINO or FC (BIII)**

Chowdhary A, et al., Clin Microbiol Infect, 2014

## Recommendations for treatment-III

- **Bone & joint:** Surgery PLUS ITC 400mg or POS 800mg or Liposomal AMB 3mg/kg (BIII)
- **Peritonitis:** Catheter removal PLUS systemic antifungal therapy (AII)
- **Disseminated infection:** Liposomal AMB 3mg/kg, ITC 400mg, VRC 400mg, POS 800mg, combination: VRC 400mg, POS 800mg PLUS TERB 250mg PLUS CSF/Leucocyte infusion (CIII)

Chowdhary A, et al., Clin Microbiol Infect, 2014

## **An international prospective study of phaeohyphomycosis**

- **99 proven/probable cases were enrolled**
- **from 18 sites in US, Peru and Australia**
- **from Jan 2, 2009~Dec 31, 2015**

Revankar et al., OFID, 2017

## **Criteria for study inclusion**

- **Culture or PCR of a black fungus from a sterile site or BAL;**
- **Histopathology confirming the presence of pigmented fungi in tissue;**
- **Compatible clinical symptoms and signs**

Revankar et al., OFID, 2017

## Data included

- Demographic information
- Sites of disease
- Diagnosis methods
- Clinical signs & symptoms
- Underlying disease & predisposing factors
- Antifungal and/or surgical therapy and clinical outcomes

Revankar et al., OFID, 2017

## Classification of the cases

- Local superficial infection: skin and sub-cutaneous tissues
- Local deep infections: all other localized infections
- Disseminated infections: fungemia, CNS and  $\geq 2$  noncontiguous sites
- Chromoblastomycosis & mycetoma
- *S.prolificans*=*L.prolificans* were included

Revankar et al., OFID, 2017

## Clinical outcome definition

- **Primary outcome measures: all-cause mortality and clinical response at 30 days post-diagnosis**
- **Secondary outcome measures**
  - \_ All-cause mortality and clinical response at end of the follow-up
  - \_ Complete response: complete resolution of clinical and radiological finding
  - \_ Partial response: improvement in clinical and radiological findings
  - \_ Failure: disease stable or progression of infection

Revankar et al., OFID, 2017

## Therapy for phaeohyphomycosis

Therapy	No. (%)			
	Total (n = 99)	Local- Superficial (n = 32)	Local-Deep (n = 41)	Disseminated (n = 26)
<b>Monotherapy</b>				
Lipid AmB	15 (15)	4 (13)	9 (22)	2 (8)
Itraconazole	21 (16)	13 (41)	7 (17)	1 (4)
Voriconazole	32 (32)	9 (28)	14 (34)	9 (35)
Posaconazole	16 (16)	10 (31)	5 (12)	1 (4)
Isavuconazole	2 (2)	1 (3)	1 (2)	0 (0)
Fluconazole	1 (1)	0 (0)	1 (2)	0 (0)
Caspofungin	2 (2)	1 (3)	0 (0)	1 (4)
Micafungin	2 (2)	1 (3)	1 (2)	0 (0)
Terbinafine	1 (1)	1 (3)	0 (0)	0 (0)
<b>Combination therapy</b>				
Azole + terbinafine	12 (12)	2 (6)	4 (10)	6 (23)
Azole + AmB	14 (14)	1 (3)	9 (22)	4 (15)
Azole + echinocandin	2 (2)	1 (3)	1 (2)	0 (0)
Azole + 5-FC	1 (1)	0 (0)	0 (0)	1 (4)
AmB + echinocandin	1 (1)	0 (0)	1 (3)	0 (0)
Triple-drug combination	6 (6)	0 (0)	1 (2)	5 (19)
Four-drug combination	1 (1)	0 (0)	0 (0)	1 (4)
Surgery	33 (33)	6 (19)	20 (49)	7 (27)
Cryotherapy	5 (5)	5 (12)	0 (0)	0 (0)

Revankar et al., OFID, 2017

## Patients outcomes

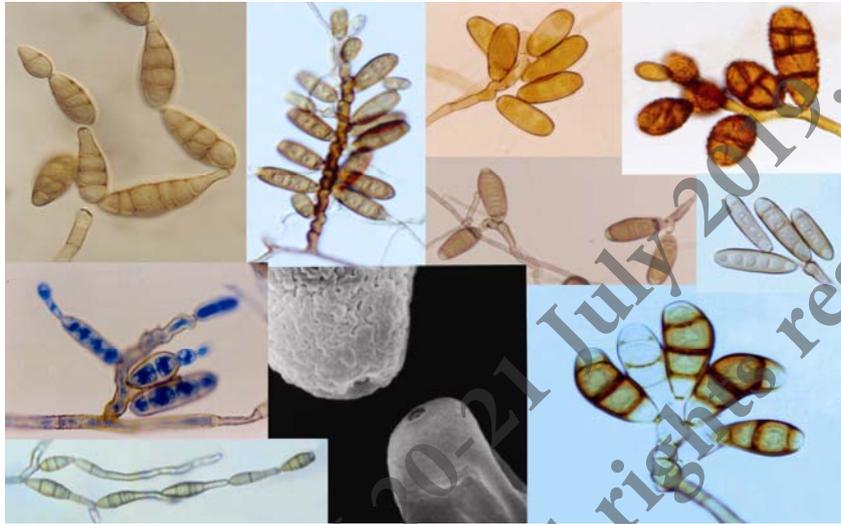
Outcome	No. (%)		
	Local-Superficial (n = 32)	Local-Deep (n = 41)	Disseminated (n = 26)
<b>30-day response</b>			
Complete	4 (13)	5 (12)	2 (8)
Partial	21 (66)	17 (41)	6 (23)
Failure	7 (22)	19 (46)	18 (69)
<b>End-of-follow-up response</b>			
Complete	16 (50)	18 (44)	3 (12)
Partial	11 (34)	10 (24)	5 (19)
Failure	5 (16)	13 (32)	18 (69)
<b>Mortality</b>			
30 d	1 (3)	5 (12)	10 (38)
End of follow-up	2 (6)	13 (32)	18 (69)
Due to fungal infection	0 (0)	4 (10)	13 (50)
Follow-up, median (range), d	189 (14–1006)	130 (2–1155)	69 (1–1104)

Revankar et al., OFID, 2017

## The *in vitro* antifungal susceptibility testing

**not been standardized nor are the  
validated MIC breakpoints**

## Different pathogenic fungi



## Pathogenic Black Fungi

- *Alternaria* spp. - *A. alternate*, *A. infectoria*)
- *Aureobasidium* spp. - *A. melanogenum*, *A. pullulans*
- *Bipolaris* spp. - *B. hawallensis*, *B. spicifera*
- *Cladophialophora* spp. - *C. carrionii*, *C. bantiana*, *C. emmonsii*
- *Curvularia* spp. - *C. lunata*, *C. geniculata*, *C. intermedia*
- *Chaetomiu* spp. - *C. globosum*, *C. funiculum*, *C. murorum*
- *Ochroconis* spp. - *O. musae*, *O. tshawytschae*, *Verruconis gallopava*
- *Drechslera* spp. - *D. biseptata*
- *Exophiala* spp. - *E. dermatitidis*, *E. jeanselmei* complex, *E. moniliae*, *E. spinifera*
- *Hortaea werneckii*
- *Exserohilum* spp. - *E. rostratum*, *E. longirostratum*, *E. mcginnisii*
- *Fonsecaea* spp. - *F. pedrosoi*, *F. monophora*, *F. nubica*,
- *Phialophora* spp. - *P. verrucosa* complex, *P. europaea*
- *Phaeoacremonium parasitica*
- *Piedraia*: spp. - *P. hortae*
- *Rhinoctadiella* spp. - *R. aguaspersa*, *R. atrovirens*, *R. mackenziei*
- *Veronaea botryosa*
- *Corynespora cassiicola*

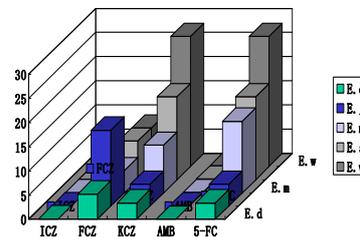
## MIC determination of black fungi

Organism	AmB	5-FC	Itra	Posa	Vori	Isavu	Caspo	Mica	Anid	Terb
<i>Alternaria</i> spp.	0.5	>64	0.5	≤0.03	1	2	2	0.5	4	1
<i>Cladophialophora bantiana</i>	8	0.25	0.25	0.125	0.125	0.125	4	4	4	0.03
<i>Curvularia lunata</i>	0.25	>64	1	0.125	4	1	8	8	4	0.06
<i>Curvularia spicifera</i>	1	>64	0.5	0.125	1	8	1	2	8	0.125
<i>Exophiala</i> spp.	2	1	0.25	0.06	0.06	0.5	2	8	4	<0.03
<i>Exophiala oligosperma</i>	1	0.25	0.125	≤0.03	0.5	2	4	4	2	0.125
<i>Fonsecaea pedrosoi</i>	8	32	0.5	0.25	0.125	0.125	8	>16	16	<0.03
<i>Fonsecaea pedrosoi</i> (#2)	8	4	0.5	0.5	0.5	0.5	2	>16	4	<0.03
<i>Lomentospora prolificans</i>	>16	>64	>16	>16	>16	>16	16	>16	8	16
<i>Lomentospora prolificans</i> (#2)	>16	>64	>16	>16	>16	>16	16	>16	8	8
<i>Lomentospora prolificans</i> (#3)	16	>64	>16	>16	16	>16	16	>16	4	4
<i>Microsphaeropsis arundinis</i>	0.5	32	≤0.03	≤0.03	0.125	0.06	8	8	16	0.25
<i>Phaeoacremonium sphinctrophorum</i>	1	8	4	0.5	0.5	2	16	>16	4	0.25
<i>Pleurostomophora richardsiae</i>	4	4	1	0.5	0.5	0.5	4	>16	1	0.125
<i>Scopulariopsis brevicaulis</i>	16	>64	>16	>16	>16	>16	8	2	2	0.5
<i>Verruconis gallopava</i>	2	2	0.5	0.25	1	16	4	<0.03	<0.03	<0.03

Abbreviations: 5-FC, flucytosine; AmB, amphotericin B; anid, anidulafungin; caspo, caspofungin; isavu, isavuconazole; itra, itraconazole; mica, micafungin; posa, posaconazole; terb, terbinafine; vori, voriconazole.

Revankar et al., OFID, 2017

## Five Antifungal Agents Against *Exophiala* spp.



Li, DM et al. Chin Med J, 1999

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

Antifungals	GM	MIC Range	MIC <sub>90</sub>
ANI	0.06	<0.015->8	0.25
AMB	0.21	<0.03-2	1
CAS	0.89	0.25-2	1
ITC	0.63	<0.03-4	1
FLU	38.7	4->64	>64
FC	>64	>64	>64
MIK	0.05	<0.015-0.125	0.125
POS	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  
81 isolates of *C.carrionii* (mg/L)**

Antifungals	GM	MIC Range	MIC <sub>50</sub>	MIC <sub>90</sub>
AMB	2.643	0.5-8	2	8
FLU	25.04	4-64	32	64
ITC	0.03	0.008-0.125	0.031	0.063
VRC	0.148	0.016-1	0.125	0.25
POS	0.025	0.016-0.063	0.016	0.063
ISA	0.136	0.016-1	0.125	0.25
CSP	1.367	0.25-4	2	2
MIK	0.296	0.016-8	0.25	4
TERB	0.049	0.008-1	0.031	0.125

Deng S, et al., *Antimicrob Agents Chemother*, 2013

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

Antifungals	GM	MIC Range	MIC <sub>50</sub>	MIC <sub>90</sub>
AMB	0.7	0.125-2	1	1
FLU	35.14	16-64	32	64
ITC	0.064	<0.016-0.25	0.063	0.125
VRC	0.769	0.125-4	1	2
POS	0.044	<0.016-0.25	0.031	0.125
ASV	0.259	0.008-1	0.25	0.5
CAS	2.551	1-8	2	4
ANI	0.073	0.016-4	0.063	2

Badali H, et al. *J Clin Microbiol*, 2010

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

Antifungals	GM	MIC Range	MIC <sub>90</sub>
AMB	28.36	8-32	32
ITC	7.00	1-32	32
POS	18.23	0.5-32	32
VRC	11.09	2-32	32
ANI	3.93	0.015-32	4
CAS	7.90	1-32	4
MIK	0.22	0.06-0.5	0.25
TERB	0.03	0.015-0.025	0.02

Giraldo A, et al. *J Clin Microbiol*, 2014

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

Antifungals	MIC Range	MIC <sub>50</sub>	MIC <sub>90</sub>	GM
AMB	0.125-4	0.25	0.5	0.54
FC	0.5-64	4	32	11.53
FLU	4->64	64	>64	52.22
ITC	0.016-4	0.125	0.5	0.40
VRC	0.5-2	1	2	1.06
POS	<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

Seyedmousavi S, et al. *Antimicrob Agents Chemother*, 2014

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

Antifungals	MIC Range	GM	MIC <sub>50</sub>	MIC <sub>90</sub>
AMB	0.12-2	1.19	1	2
FC	0.12-64	0.24	1	4
VRC	0.015-1	0.06	0.06	0.25
ITC	0.015-1	0.05	0.06	0.25
TERB	0.015-0.25	0.02	0.015	0.03

Duarte AP, et al. *Mycopathologia*, 2013

### MICs of different antifungals against 48 isolates of *P. verrucosa* (mg/L)

Strain group (no. of strains) and drug	MIC/MEC ( $\mu\text{g/ml}$ )			Geometric mean
	Range	50%	90%	
Total ( $n = 46$ )				
Fluconazole	8–256	32	64	55.826
Flucytosine	2–256	16	64	32.609
Amphotericin B	2–4	4	4	3.261
Itraconazole	0.25–4	0.5	2	0.973
Voriconazole	0.063–4	0.25	1	0.58
Posaconazole	0.031–1	0.125	0.5	0.232
Caspofungin	2–16	8	16	9.174
Micafungin	0.5–32	4	16	8.63
Terbinafine	0.002–1	0.125	0.25	0.152

Li Y, et al. AAC, 2014

### ITZ 200mg/day for 2 months



Case of Prof. Liyan Xi

**Chromoblastomycosis treated by ITC  
for 4 months**



**ITZ 200mg/day for 18 months**



before

after

## Patient treated by TBRF

(250mg bid)



**Before treatment**

- 病原菌: *F. monophora*
- First:
  - Combination therapy with TBF (250mg,bid) and bifonazole x3w
  - 明显改善
  - 皮损直接经济及培养 (-)
- Then:联合应用TBF (250mg,bid) 和联苯苄唑至今

**After treatme**



Case of Prof. Liyan Xi

## Combination with ITZ & TBF




**Before treatment (A, B, C)**

- ◆ 病原菌: *F. monophora*
- ◆ ITZ + TBF:  
Itraconazole: 200mg qd  
Terbinafine: 250mg qd x4 w
- ◆ After 4 weeks:  
Terbinafine only  
250mg qd x3w
- ◆ 总疗程: 7 w

**After treatment (D, E)**

Case of Prof. Liyan Xi

## Combination with ITZ+TBF

**Before treatment**

- 病原菌: *F. monophora*
- ITZ+TBF:  
Itraconazole:  
200mg qd  
Terbinafine:  
250mg qd ×4 w
- After 4 weeks:  
Terbinafine only  
250mg qd ×6w
- 总疗程: 10 w



Case of Prof. Liyan Xi

## ITZ + Surgery



Chromoblastomycosis caused by *C. carrionii*

## Antifungals plus PDT



**Before treatment**

- 病原菌: *F. monophora*
- First: Antifungal agents
  - Single use with ITZ or combination therapy with ITZ and TBF
  - 轻度改善, 后复发
- Then:
  - ALA-PDT therapy ×8 times
  - TBF 500mg/d ×3m
  - 明显改善
  - 皮损直接经济及培养 (-)
- Finally: 单独使用TBF 500mg/d 至今

**After treatment**



Case of Prof. Liyan Xi

## Antifungals +PDT



**Before treatment**

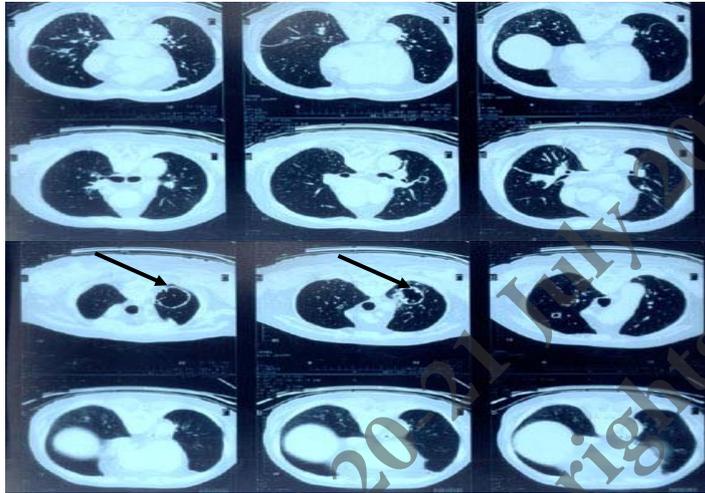
- 病原菌: *F. monophora*
- First: Antifungal agents
  - Single use with ITZ or combination therapy with ITZ and TBF ×18m
  - Moderate improvement, relapse
- Then: ALA-PDT therapy
  - 4 times (in 4m)
  - 明显改善, 后复发
- Finally: TBF 250mg, bid 至今

**After treatment**



Case of Prof. Liyan Xi

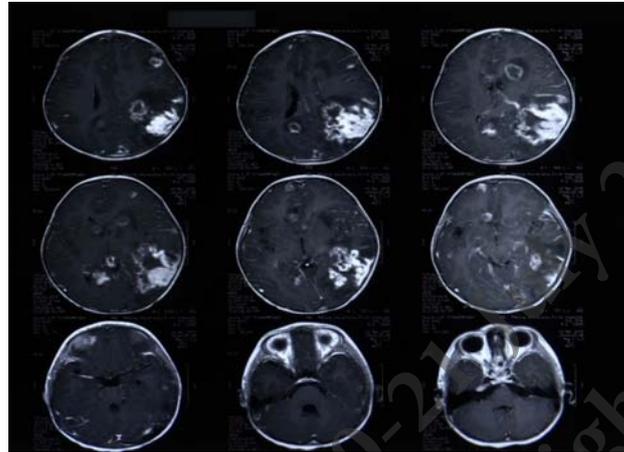
**Phaeohyphomycosis of the lung caused by  
*Verruconis gallopavum***



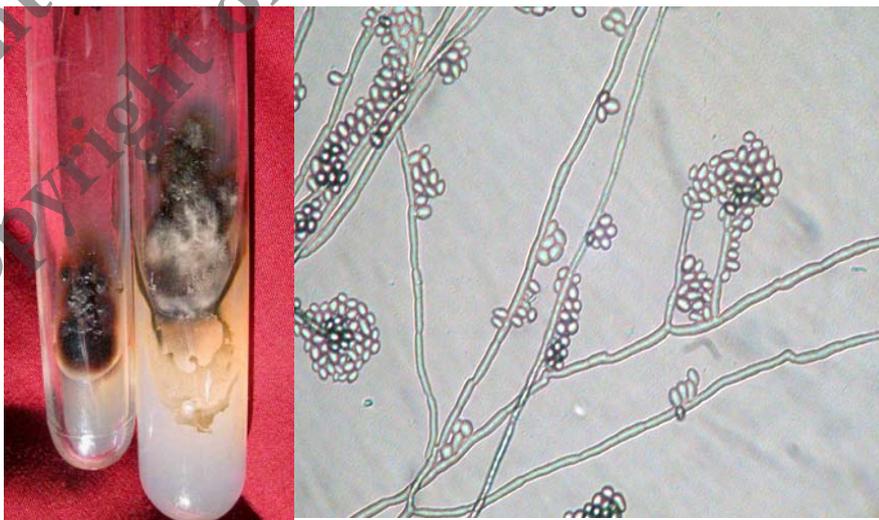
***Verruconis (Ochroconis) gallopavum* (Cooke)**



### MRI of the cerebral abscess



### Fungal Culture: *E.dermititidis*



## Challenges of treatment

- The huge diversity of the black fungi and their host range
- Length of therapy and choice of intervention (surgery, antifungals or both) based on the clinical presentation, underlying condition and the initial response
- The prolonged duration of therapy ranges from several weeks to months or longer
- **Especially difficult in the immunosuppressed patients- new strategies such as immunologic method are needed**

Chowdhary A, et al., Clin Microbiol Infect, 2014

### Fetal Case of Phaeohiphomycosis due to CARD9 deficiency



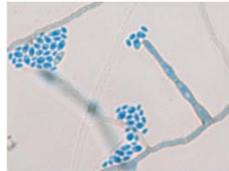
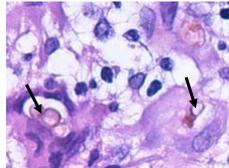
2006      2009      2011      2015...



Disseminated lesions in 2015, with deafness, perforation on the palate, and mental and psychological disorder (manic & dementia state). The patient passed away in 2016.

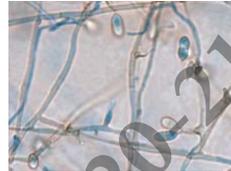
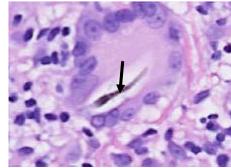
**Phaeohyphomycosis due to 3 other dematiaceous fungi**

P1



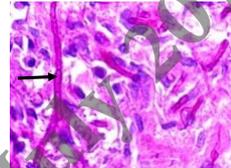
*Exophiala spinifera*

P2



*Ochroconis musae*

P3



*Corynespora cassiicola*

Xiaowen Wang, et al. *J Invest Dermatol.* 2018.

