CNS Mould Infections: Etiologic Agents and Their Identification

Deanna A Sutton, PhD
MT, SM(ASCP), RM, SM(NRCM)
Fungus Testing Laboratory
University of Texas Health Science Center at San Antonio
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Speaker: Deanna A Sutton
“Nothing to disclose”.
Outline

• CNS disease in the “Healthy” host
  – Specific categories of disease
  – Genera/species – their identification

• CNS disease in the immunocompromised host
  – Selected genera/species reported in the literature – their identification
THE PATIENT

• Disease occurs in two types of patients
  – Healthy
  – Immune compromised
The Immunocompetent or Non-compromised Host

• Absence of any concomitant or previous chronic disease
  – Diabetes mellitus
  – Renal failure
  – Cirrhosis
  – Malignancy

• No history of
  – Intravenous drug abuse
  – Use of immunosuppressive or corticosteroid therapy
  – Organ transplantation
  – HIV infection

• No clinical or radiologic evidence of systemic fungal disease
Exclusions

• Rhino-orbital-cerebral mucormycosis
  – Several genera of Mucorales in compromised patients

• Mucorales common in immunocompetent host sustaining trauma but usually not in the CNS
  – Apophysomyces and Saksenaea spp.
Exclusions

• Dimorphic pathogens

• Other organisms not generally considered neurotropic but that have been occasionally recovered from the brain in compromised patients

• Questionable case reports not supported by culture

• Isolates in case reports not identified to the species level
The “Typical, Healthy” Patient
(some common features)

– No known risk factors
– *May* reside in temperate or tropical climate
– Has an unrecognized or poorly characterized immunodeficiency
– Trauma, accidental or surgical
– Extension from contiguous areas like the nasal sinus
– Near-drowning
How best to stratify?

• The patient
• Major categories of disease?
• Site of infections within the CNS?
• By fungal class or group?
• Geographic locale?
• Hyaline vs. dark?
• Frequency of recovery?
• Use a **COMBINATION** of the above
Categories of CNS disease in immunocompetent patients

- Primary CNS Phaeohyphomycosis
- Craniocerebral aspergillosis
- Primary CNS Mucormycosis
- CNS phaeohyphomycosis by non-Chaetothyrialean fungi
- Near-drowning CNS disease
PRIMARY CNS PHAEOHYPHOMYCOSIS


• Revankar et al. 2004. Primary central nervous system phaeohyphomycosisa review of 101 cases. CID 38:206-16

PRIMARY CNS PHAEOHYPHOMYCOSIS

• Primary neurotropic Chaetothyrialean agents
  – *Cladophialophora bantiana*
  – *Cladophialophora modesta*
  – *Rhinocladiella mackenziei*
  – *Exophiala dermatitidis*
  – *Exophiala asiatica*
Different areas of involvement within the CNS

Blue – meningitis
Yellow – cerebritis (within brain parenchyma – abscesses)
Red arrows – rhinocerebral
Orange – lymph node
Green – CSF involvement

Figure from Horré R & GS deHoog, 1999. Primary cerebral infections by melanized fungi: a review. Stud Mycol 43:180
Geographic distribution of melanized primary neurotropic agents

Blue stars
*Rhinocladiella mackenziei*

Green triangles
*Exophiala dermatitidis*

Red circles
*Cladophialophora bantiana*

Figure from Horré R & GS deHoog, 1999. Primary cerebral infections by melanized fungi: a review. Stud Mycol 43:180
Cladophialophora bantiana

- World-wide distribution
- Acquisition probably pulmonary
- Multiple granulomatous abscesses
- Long, sparsely-branched conidial chains
- Growth at 40°C
- Mycosel +, urease +
- 76 FTL isolates
  (2000 – 2012)
**Cladophialophora modesta**

- Single case reported in a mill worker – USA, North Carolina
- Possibly acquired traumatically – received scalp laceration from iron pipe 4 mos. previously
- Sparse conidial production
- Chains of 3-7 conidia
- Growth above 40°C

Rhinocladiella mackenziei

- Commonly seen in Middle East
- New cases in India (diabetes), Afghanistan (colon cancer), Pakistan (6 cases)
- Neurotropic, brain abscesses
- Slow growth
- AMB resistance – survival in one patient receiving POSA

Badali et al., 2010, JCM 48:646-649
Cristini et al., 2010, JCM 48:3451-3454
Jabeen et al., 2011, CID 52:213-217
**Exophiala dermatitidis**

- CNS disease geographically restricted - East and Southeast Asia – tropics
- Often younger patients – granulomatous lesions
- Growth at 40ºC, nitrate negative
- Thermotolerance, acid tolerance, melanization, capsular yeasts, osmotolerance
- Suggested acquisition through intestinal tract supported by one patient with concomitant diarrhea with *E. dermatitidis*
- More chronic in nature

**Exophiala asiatica**

PRIMARY CNS ASPERGILLOSIS

• (25 cases)


Eurotiales

Aspergillus flavus
Large conidia - sinusitis
Extension from sinus
Rare space occupying intracranial lesions
Extensive fibrosis prevents drug penetration
Need extensive radical excision
Tropical climates
  India, Pakistan, Sudan, Saudi Arabia
PRIMARY CNS ASPERGILLOSIS

CT SCANS


GRANULOMA
Post-traumatic head injury in an immunocompetent patient *Absidia corymbifera* (as reported at that time) UK

56-y-o male struck with a pickaxe at a construction site

CSF and serum contained precipitating antibodies against antigens of the *A. corymbifera* isolate in the CSF

SECONDARY CNS PHAEOHYPHOMYCOSIS

CNS Phaeohyphomycosis by non-Chaeotothyrialean fungi

- *Cladosporium cladosporioides* (Capnodiales), Turkey
- *Nodulisporium* sp. (Xylariales), India
- *Curvularia clavata* (Pleosporales), USA
- *Neoscytalidium dimidiatum* (Botryosphaeriales), Pakistan

(Neurotropic? – both species grow at 50ºC)

- *Myceliophthora thermophila* (Sordariales), Canada
- *Thielavia subthermophila* (Sordariales), India


Nodulisporium sp.


Resection of lesion

Hyphae in brain tissue  Branched conidiophores, denticles, & conidia
Myceliophthora thermophila

- 21-mo-old male
- Penetrating head injury in a barnyard
- Abscess resected 6 wks after injury
- Received AMB and ITR
- Child well, neurologically intact 6 mos after excision

Fatal cerebral phaeohyphomycosis in a immunocompetent individual due to *Thielavia subthermophila*

*Thielavia subthermophila* (CBS 125981)

- Farmer, northern India
- No history of any trauma, near-drowning, or similar predisposing factors

NEAR-DROWNING CNS SCEDOSPORIOSIS
Microascales

• Members of the *Pseuallescheria boydii* complex (mostly *P. boydii* and *P. apiosperma*)
  – Near-drowning encephalitis

NEAR-DROWNING CNS ASPERGILLOSIS

Eurotiales

• Warm, humid weather
• 10-mo-old healthy girl lying face down in pond water for +5 min
• Day 6 – endotracheal aspirate grew A. fumigatus
• Day 7 onward – pulmonary condition worsened
• Day 12 – epilepsy
• Day 14 – CT of brain and lungs; open brain Bx, A fumigatus
• Day 16 – expired
• Two other adult patients reviewed in this report – 3 cases due to Aspergillus fumigatus

A, Chest radiograph on days 2, 6, 9, and 12.

B. HRCT lungs, day 14
C. CT of brain, day 14
D. MRI of brain, day 14

Summary of CNS disease in immunocompetent patients

• Primary CNS Phaeohyphomycosis
• Craniocerebral aspergillosis
• Primary CNS mucormycosis
• CNS phaeohyphomycosis by non-Chaetothyrialean fungi
• Near-drowning CNS disease

(List of agents discussed is not all-inclusive)
CNS DISEASE IN COMPROMISED HOSTS

Selected Cases

• Neurotropic organisms that occur almost exclusively in compromised individuals
  – *Ochroconis gallopava*
  – Thermotolerant *Chaetomium* spp.
  – *Achaetomium strumarium*
  – *Fonsecaea monophora*
CNS DISEASE IN COMPROMISED HOSTS

Selected Cases

• Organisms not generally considered neurotropic but that have been occasionally recovered from the brain in compromised patients
  – *Scedosporium prolificans*
  – *Acrophialophora fusicpora*
TWO PATIENTS – SAME ORGANISM

• Patient # 1 – Type II diabetes mellitus, maintained tropical aquaria as hobby and handled tropical fish and plant – present with brain lesion

• Patient # 2 – Awaiting a lung transplant
Patient # 1 Excised lesion

- Excised brain tissue at this time was that of an abscess with a necrotic center and dense fibrous tissue capsule
- Brown septate branching hyphae, some moniliform elements
- Cellular infiltration by neutrophils, foamy macrophages, lymphocytes and multinucleated giant cells
PATIENT # 1

GMS stain, lesion at 3 mos

Patient # 1 Recovery of organism

- Aspirate cultured onto bacterial and fungal media at 27 and 37°C
- After 7 days, a dark fungus was growing on the SDA

PFA, 25°C, 14 days
Moderate growth rate
Spreading
Velvety
Olivaceous
Outcome

• Resection of lesions and antifungal therapy (ITRA, 5-FC)
• MRI 12 mos after resection showed good resolution of lesion
• Antifungal therapy stopped 21 mos after the initial diagnosis
PATIENT #2

- Female, Houston
- Awaiting lung transplant
- Same organism recovered from lesions on leg and a brain abscess
Black mould where conidiation may be of three types?

- *Fonsecaea* spp.
  - *Cladosporium*-like type
  - *Rhinocladiella*-like type
  - *Phialophora* type (occasionally to rarely)
Fonsecaea pedrosoi

Chromoblastomycosis – Clinical Presentation

- Chromoblastomycosis characterized by raised, verrucous, cauliflower-like lesions
**Fonsecaea pedrosoi**

Histopathology

- Hyphae in tissue divide by septation in more than one plane
- Produce hyphal structures referred to as “sclerotic” bodies
Back to our cases....

- 50 strains (including reference strains) of fungi with *Fonsecaea*-like morphology studied by the CBS – included *F. pedrosoi* and *F. compacta*
  - Morphology
  - Physiology
  - Molecular
- Unable to distinguish *F. pedrosoi* from *F. compacta* – a morphologic variant
- Did distinguish two separate clades by ITS sequence data
Phylogenetic tree of *Fonsecaea* on confidently aligned ITS rDNA sequences

*F. pedrosoi*

*F. monophora*

Fonsecaea monophora

- Case isolates identified as *F. monophora* by sequencing of rDNA ITS region & comparison with CBS data base

- What’s significant about this?

- Older literature reports *F. pedrosoi* from brain
  - Middle East cases reidentified as *Rhinocladiella mackenziei*
  - South American cases reidentified as *F. monophora*
Fonsecaea monophora

• *F. pedrosoi*
  – Pathogen strictly associated with chromoblastomycosis

• *F. monophora*
  – Associated with chromoblastomycosis *and* exhibits marked neurotropism
  – 4 of the 12 isolates studied involved primary brain infection
**Fonsecaea monophora**

- Natural habitat may be putrid plant material as several strains from dead plants and soil were identified as this species.
- Geographic distribution mainly tropical South America and Africa.
- Source of organism may have been South American fish and/or South-east Asian aquatic plants handled by patient who maintained tropical aquaria as a hobby.
Slight morphologic differences

**F. monophora**

Chains of up to 3 conidia; longer than *F. pedrosoi*

May also have multi-celled, sessile conidial chains as in the genus *Cladophialophora*

**F. pedrosoi**

Shorter chains and longer denticles

de Hoog et al, *Medical Mycology* 2004;42:405-416
Not separated by physiologic tests

• Shared physiologic traits include
  – Intolerance to 10% NaCl
  – Tolerance to cycloheximide
  – Growth at 37°C
  – No growth at 40°C
References

• de Hoog et al. 2004. Molecular ecology and pathogenic potential of *Fonsecaea* species. *Medical Mycology*; 42:405-416


**Ochroconis gallopava**

- Colonies reddish-brown to brownish-black with a mahogany diffusible pigment
  - Better on SDA
- Neurotropic – thermophilic - 42°C
- Conidiogenous cells with denticles – bear 1 or 2 2-celled conidia
  - Larger cell at apex (clavate)
- No growth on Mycosel™; urease +
Ochroconis gallopava

PFA
SDA

Photo courtesy of Nancy McClenny
Ochroconis gallopava

Conidiophores, denticles, and clavate, two-celled conidia
Acrophialophora fusispora

- May be misidentified as *Scedosporium prolificans*
- Neurotropic
- Growth at 42°C
- Several case reports – keratitis, cystic fibrosis patients
Acrophialophora fusicapora

Acrophialophora fusicapora Brain Abscess in a Child with Acute Lymphoblastic Leukemia: Review of Cases and Taxonomy


![Image of fungal growth and electron microscopy of spores.](image-url)
Acrophialophora fusispora

Airway Colonization by Acrophialophora fusispora in Patients with Cystic Fibrosis

Bernard Clmon,1* Svetlana Challier,2 Hugues Béguin,3 Jacqueline Camère,4 Dominique Chabasse,1 and Jean-Philippe Bouchara1

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Acrophialophora fusiclora

Key Microscopic Features

Collapsed conidiophores

Typical tape mount after several days incubation (5-7 days)
**Acrophialophora fusiclpora**

Key Microscopic Features

- Conidiophore with terminal conidia
- Inflated phialides – conidia in chains, young brown conidiophore
- Inflated phialides – conidia in chains
Scedosporium prolificans

- Similar morphologically/microscopically to *Scedosporium apiospermum*
- Anellides are flask-shaped/swollen at base
- Growth at 40°C; no growth on Mycosel™
- Extremely refractory to antifungal therapy
- Disseminated infections usually fatal
**Scedosporium prolificans**

Basally inflated conidiogenous cells with single or multiple oval conidia at their tips

Conidia never in chains, unlike for *A. fusispora*
Review

• CNS Disease in “healthy” patients
• CNS Disease in Immune Compromised patients
  – Should consider likely organisms at outset based on patient’s clinical Hx
  – Consider fungal CNS disease an “emergency” although it may have developed over time
  – Provide clinicians preliminary reports as appropriate
CNS DISEASE IN “HEALTHY” PATIENTS

- Primary CNS Phaeohyphomycosis
- Craniocerebral aspergillosis
- Primary CNS mucormycosis
- CNS phaeohyphomycosis by non-Chaetothyrialean fungi
- Near-drowning CNS disease

List is not all-inclusive
CNS DISEASE IN IMMUNE COMPROMISED PATIENTS  Selected organisms

- *Fonsecaea monophora*
- *Ochroconis gallopava*
- *Acrophialohora fusicapora*
- *Scedosporium prolificans*
Updated information on http://www.cdc.gov/hai/outbreaks/meningitis.html

Ongoing Investigation: Three lots of steroid solution with preservative-free methylprednisolone acetate solution were used to treat both peripheral joint and back pain manufactured from a Massachusetts company since May 2012.

Almost 14,000 persons received epidural steroid injections with preservative-free methylprednisolone acetate solution.

As of 10/15, 233 Cases (231 fungal meningitis cases plus 2 peripheral joint infections)

15 States
15 Deaths
Thank you!