Unusual mould infections

Dr. Alida Fe Talento
St. James’s Hospital
Dublin Ireland
St. James’s Hospital

Biggest tertiary referral centre in Ireland
National Bone Marrow and Stem Cell Transplant Unit
National Burns Unit
Mixed speciality Critical care Unit
64 M

Post RM and RL lobectomy for Non-small cell lung CA
Complicated post-op course
Air leak
HAP
Discharged after 1 month
Re-admitted 2 days later
64 M

VATS procedure
Empiric meropenem and vancomycin
Blood, sputum, urine and tissue samples – Nil growth

Day 23 post-readmission
Drain fluid received in laboratory
Mould isolated – identified as *Rhizopus oryzae*

Consult with Microbiology team –
De-escalate to pip-tazobactam

Ward review
Isolation of moulds/fungal pathogens from non-sterile site clinical samples should be interpreted as significant until proven otherwise.

Agree? Disagree? Not sure?
Microbiologists’ Dilemma

Isolation of moulds/fungal pathogens from cultures is not easy to interpret
Consider – type of sample; how it was taken; transport; culture conditions
Direct microscopy is helpful

Positive culture has a low PPV of invasive mucormycosis
Interpret with caution

A. Borman and E. Johnson
Current Fungal Infection Reports September 2014

M. Torres-Narbona et al
Medical Mycology 2008
## Fungal cultures

<table>
<thead>
<tr>
<th>Fungi*</th>
<th>N</th>
<th>Sample type</th>
<th>Received antifungal therapy</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhizopus oryzae</td>
<td>6¹</td>
<td>Respiratory sample</td>
<td>1</td>
<td>Also had <em>A. fumigatus</em> in same sample</td>
</tr>
<tr>
<td>Scedosporium apiospermum</td>
<td>3</td>
<td>Respiratory sample</td>
<td>2</td>
<td>One also had <em>A. fumigatus</em></td>
</tr>
<tr>
<td>Scedosporium prolificans</td>
<td>2</td>
<td>Blood (1) Respiratory sample (1)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Geotrichum capitatum</td>
<td>3</td>
<td>Respiratory sample</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td><em>Trichosporon asahii</em></td>
<td>3</td>
<td>Line tip and tissue (2) Blood (1)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cladosporium sp</td>
<td>5</td>
<td>Respiratory sample</td>
<td>1</td>
<td><em>Also had Exophiala sp</em></td>
</tr>
<tr>
<td>Scopulariopsis sp</td>
<td>1</td>
<td>Respiratory sample</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Chrysonila sitophila</td>
<td>1</td>
<td>Respiratory sample</td>
<td>Nil</td>
<td></td>
</tr>
</tbody>
</table>

Retrospective review of fungal cultures from clinical samples in SJH in the last 5 years

*Candida, Cryptococcus* and *Aspergillus* spp excluded

¹ Case patient excluded
Clinical progress

Patient stable
Decision – not to start antifungal therapy
Antimicrobials de-escalated
Drains removed

Day 46 – clinical deterioration
Clinical progress

New drain inserted
Culture – *Rhizopus oryzae*

Liposomal amphotericin B started
Multi-disciplinary team approach
Day 52 - Pleural washout and biopsy
## Antifungal Susceptibility

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>SJH MIC (E-Test)</th>
<th>Mycology Reference Lab MIC (Broth microdilution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin</td>
<td>0.125</td>
<td>0.25</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>ND</td>
<td>2</td>
</tr>
</tbody>
</table>

### Issues
- No established clinical breakpoints (EUCAST and CLSI)
- Amphotericin B – first line agent
- Posaconazole – Salvage therapy
- ? Combination therapy

Isavuconazole – new triazole agent licensed for invasive aspergillosis and mucormycosis
Clinical progress

Remained unwell
CPE *E. cloacae* from sputum samples

Day 70 –
LAmB, meropenem, colistin (3 weeks)

Close monitoring of renal and liver function
Further pleural washouts, window created
Day 70

What would you have done?
A. Continue current management
B. Add posaconazole to current antimicrobial therapy
C. Add isavuconazole to his antimicrobial therapy
D. Stop L-AmB, change to posaconazole
Patient’s progress

Posaconazole was added, dose guided by therapeutic drug monitoring

Slowly improved, antibiotics were discontinued

Received 3 months of antifungal therapy
Full recovery
Phylum Glomeromycota

<table>
<thead>
<tr>
<th>Subphylum</th>
<th>Genus</th>
<th>Species most frequently isolated from patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucormycotina</td>
<td>Apophysomyces</td>
<td>A. variabilis</td>
</tr>
<tr>
<td></td>
<td>Cunninghamella</td>
<td>C. bertholletiae</td>
</tr>
<tr>
<td></td>
<td>Lichtheimia (Absidia)</td>
<td>L. corymbifera</td>
</tr>
<tr>
<td></td>
<td>Mucor</td>
<td>L. ramosa</td>
</tr>
<tr>
<td></td>
<td>Rhizopus</td>
<td>M. circinelloides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R. arrhizus (oryzae)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R. microsporus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R. pusillus</td>
</tr>
<tr>
<td>Entomophthoromycotina</td>
<td>Saksenaea</td>
<td>S. vasiformis</td>
</tr>
<tr>
<td></td>
<td>Basidiobolus</td>
<td>B. ranarum</td>
</tr>
<tr>
<td></td>
<td>Conidiobolus</td>
<td>C. coronatus</td>
</tr>
</tbody>
</table>

TABLE 1. Classification of clinically relevant fungi formerly regarded as ‘zygomycetes’ [9,13]

U Binder et al CMI 2014
# Invasive mucormycosis

## TABLE 1. Overview of the main European studies on mucormycosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Study category</th>
<th>No of patients</th>
<th>Incidence</th>
<th>Laboratory diagnosis</th>
<th>Case fatality rates %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greece</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torres-Narbona [6]</td>
<td>2005</td>
<td>Multicentre prospective</td>
<td>6</td>
<td>0.43/10^6 inhab. or 0.62/10^5 hosp. admissions in 2005</td>
<td>Histopathology culture</td>
<td>nd</td>
</tr>
<tr>
<td>Spain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bitar [1]</td>
<td>1997–2006</td>
<td>Multicentre retrospective</td>
<td>531</td>
<td>Increase 0.7/10^6 inhab. in 1997 to 1.2/10^6 inhab. in 2006</td>
<td>nd</td>
<td>47.8–4.2 according to underlying disease</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saegeman [2]</td>
<td>2000–2009</td>
<td>I centre retrospective</td>
<td>31</td>
<td>Increase 0.019/10^6 patient-days in 2000 to 0.148/10^6 patient-days in 2009</td>
<td>Histopathology or culture</td>
<td>11–60, (according to underlying disease)</td>
</tr>
<tr>
<td>Belgium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pagano [7]</td>
<td>2004–2007</td>
<td>Multicentre prospective</td>
<td>60</td>
<td>nd</td>
<td>Histopathology or culture</td>
<td>53 total 73 antifungals only</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14 antifungals + surgery</td>
</tr>
<tr>
<td>ECMM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>non-ID</td>
</tr>
</tbody>
</table>

nd, not defined; ECMM, European Confederation of Medical Mycology.

G. Petrikkos et al CMI 2014
Invasive mucormycosis

Emerging risk factors
- Natural disasters, burns, voriconazole prophylaxis

Clinical presentation
- Variable
- Pleural space infection – unusual

How did he get the infection?
- Contaminated bandages, linen, tongue depressors

U. Binder et al CMI 2014
G. Petrikkos et al CMI 2014
G. Petrikkos et al CID 2012
V. Cheng et al CID
Hope you can interpret this succinctly and give a message

Risk factors

Emerging risk factors
Natural disasters
Burns
Azole prophylaxis

U. Binder et al CMI 2014
G. Petrikkos et al CMI 2014
FIG. 2. Distribution of clinical presentation according to study. The most prominent clinical forms are presented. ‘Others’ represents gastrointestinal or solitary organ infection (brain, heart, kidney, peritoneum, liver, biliary tract and spleen). ‘Disseminated’ represents infection with concurrent involvement of at least two noncontiguous organ sites of the body. *Data of only six cases. **Possible bias due to the nature of the study.

U. Binder et al CMI 2014
G. Petrikkos et al CMI 2014
Diagnosis

Culture from sterile sites – microscopy and colonial morphology

Histopathology

New technologies

Maldi-TOF

PCR – serum, tissues

Mucorales specific T-cell detection
Management

Multi-disciplinary team approach

Source control

Control of underlying conditions

Antifungal therapy

Therapeutic drug monitoring

Optimum Duration

F. Tissot et al ECIL – 6 Guidelines
Haematologica 2017
A. Katragkou et al CMI 2014
83F

Histopathologist –
Fungal hyphae from sinus biopsy

History of epistaxis, proptosis, facial pain
Non-neutropaenic, non-immunocompromised

ENT – maxillary mass
Malignancy vs fungal infection

Culture – *A. fumigatus*
MIC
Voriconazole – 0.125
Posaconazole – 0.125
Amphotericin – 0.125
Her journey

Voriconazole
5 days after starting voriconazole, LFTS were markedly deranged

What would you have done?

A. Continue voriconazole
B. Discontinue voriconazole, start L-AmB 3 mg/kg OD
C. Discontinue voriconazole, start L-AmB 5 mg/kg OD
D. Discontinue voriconazole, start posaconazole
Her journey

Voriconazole
L-AmB
WCC
Posaconazole
Fungal Rhinosinusitis

Invasive vs non-invasive
Acute vs chronic
Chronic invasive – Rare
Can occur in non-immunocompromised host
*A. fumigatus* - most common cause
Life threatening
Surgical and Medical Management

S Baeesa et al Asian J Neurosurgery 2014
K Montone H and N Pathology 2016
LC Goh et al J of Laryn and Otology 2017
A Singh et al J Clin Diag Research 2017
Her journey

Medical management
Improved, discharged on PO posaconazole
TDMs and ECGs

Re-admitted a few weeks later

Palliation
44 F

AML, post allo-BMT, GVHD
Aug 2016
Sputum: *Lomenstopora prolificans*
Treated with voriconazole for 12 weeks

Oct 2017
Sputum: *Lomenstopora prolificans*
Resistant to amphotericin, azoles and terbinafine
Would you treat her?

And if so, with what?
Learning points

Diagnostic challenges

Multi-disciplinary team management

Antifungal therapy
  Antifungal susceptibility testing
  Adverse events
  TDMs