Cryptococcosis and solid organ transplantation

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Cryptococcosis

Causa: *Cryptococcus neoformans/gattii*

- For risk factor (neoformans) = cellular immune deficiency (HIV++)
- AIDS defining illness
- 13-18% of HIV+ subjects in some African or South East Asian countries:
  - 1st cause of meningitis in the Southern part of Africa
  - 2nd opportunistic infection after TB
  - Mortality ≥ 50% within the first 15 days

Major impact of HAART
Who develops cryptococccosis

35 cases in France (1985-2001)
- 34 AIDS cases (77.4%)
- 1 HIV negative:
  - 17.4% SOT
  - 36.8% Hem malign/cancers
  - 20.4% various underlying dis
  - 25.4% no known immune deficit
Epidemiology of SOT-associated cryptococcosis (1)

Prevalence: 0.26-5%; 70.1-78% male


Incidence after anti-thymocyte Ig or alemtuzumab (anti CD-52) [Silveira, Transpl Infect Dis 2007]:
- 0.26% (2/781) if not
- 0.3% (2/646) after 1 dose
- 2.24% (3/134) after 2 doses (p = 0.03)
- Median time of occurrence 255 d (7-517 d), 14.2% mortality

Alemtuzumab used for rejection [OR = 3.5; 95% CI, 1.8-6.8] [Peleg, CID 2007]
Epidemiology of SOT-associated cryptococcosis (2)

Table incidence according to transplanted organ [Vilchez et al. Am Transplant 2002]

For transplant recipients:
- Older than others
- Earlier occurrence
- Skin and bone/joints lesions
- Increased risk of dissemination (HR 65)
- % of positive blood cultures [Singh in Transplant 1997]
Distribution of fungal species in solid organ transplanted patients with IFI in the US
C. neoformans infection pathogenesis during SOT
The interval between transplantation and IFI

Impact of anti-*C. neoformans* antibodies detection before SOT

Prévention?
Médiane: 16-21 mois
Cryptococcal Collaborative Transplant Study Group

15 original papers published since 2005 in US journals

Cryptococcosis in Solid Organ Transplant Recipients: Current State of the Science

Nina Singh, Francisco Dromer, John R. Perfect, and Olivier Lortholary

1University of Pittsburgh, Pennsylvania; 2Duke University, Durham, North Carolina; and 3Institut Pasteur, Molecular Mycology Unit, National Reference Center for Mycoses and Anthracoses, and 4University Paris Descartes, Centre d'Infectiologie Necker-Paris, Hôpital Necker-Enfants-Malades, Paris, France
Unrecognized pretransplant or donor derived cryptococcosis in SOT
Sun et al. CID, in press

Multicenter cohort: 175 (SOT) recipients with cryptococcosis

Early and late-onset cryptococcosis were defined as disease occurring ≤30 days or >30 days post-transplant, respectively.

Early-onset disease:

5%; mean of 5.7 days post-transplant.

More frequently liver transplant recipients

More frequent unusual locations [transplanted allograft and surgical fossa/site (55.6% vs. 7.2%, p<.0001)]

May have unrecognized pre-transplant or donor-derived cryptococcosis.
Draft transmitted cryptococcosis in the US

John Baddley et al. Unpublished data

<table>
<thead>
<tr>
<th>Locus</th>
<th>CAP59</th>
<th>GPD1</th>
<th>IGS1</th>
<th>LAC1</th>
<th>PLB1</th>
<th>SOD1</th>
<th>URA5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele Length</td>
<td>501</td>
<td>489</td>
<td>725</td>
<td>471</td>
<td>533</td>
<td>536</td>
<td>637</td>
</tr>
<tr>
<td>Patient 1 blood</td>
<td>8</td>
<td>10</td>
<td>15</td>
<td>8</td>
<td>12</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Patient 2 blood</td>
<td>8</td>
<td>10</td>
<td>15</td>
<td>8</td>
<td>12</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Patient 3 blood</td>
<td>8</td>
<td>10</td>
<td>15</td>
<td>8</td>
<td>12</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Patient 3 CSF</td>
<td>8</td>
<td>10</td>
<td>15</td>
<td>8</td>
<td>12</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>

ST similarities of C. neoformans isolates from 3 geographically distant
Clinical presentation of SOT-associated cryptococcosis

Impact of immunosuppressive therapy:

- Tacrolimus:

- Meningeal symptoms < 1/3 cases [Vilchez, Am J Transplant 2002] despite involvement in 60% of cases

- Pulmonary nodules ± ARDS [Vilchez, Medicine 2001]

- Primary or secondary skin lesions [Husain, EID 2001]
Cutaneous Cryptococcosis in SOT
Sun et al. Med Mycol 2010

46 (17.8%): nodular/mass (34.8%) m aculopapule (30.4%) ulcer/pustule/abscess (30.4%) cellulitis (30.4%) 2% lower extremities Localized disease in 30.8% Overall mortality at 90 d = 15.4%

146 SOT recipients
9 (88%)/146 SOT recipients with cryptococcosis with SF analysis

80 (62%) had CNS disease
increased risk of CNS disease:
- abnormal mental status,
- > 24 months post-transplantation
- CPS titer > 1:64

Lumbar puncture mandatory for these patients
2 SOT with cryptococcosis (50% with CNS involvement)

NS lesions were identified in 16/61 patients (26.3%)

- Leptomeningeal lesions in eight
- Parenchymal lesions in six
- Hydrocephalus in two

13/16 CNS lesions at diagnosis

3 CNS Immune reconstitution inflammatory syndrome

PS titers significantly higher:

- Meningeal versus parenchymal lesions
# Cryptococcosis diagnosis: extensive work up


<table>
<thead>
<tr>
<th>Test</th>
<th>Percentage of patients (n) according to HIV status</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (n = 177)</td>
<td>Negative (n = 53)</td>
<td></td>
</tr>
<tr>
<td>Blood culture</td>
<td>46 (168)</td>
<td>12 (51)</td>
</tr>
<tr>
<td>CSF culture</td>
<td>89 (176)</td>
<td>69 (42)</td>
</tr>
<tr>
<td>Urine culture</td>
<td>30.5 (154)</td>
<td>25 (52)</td>
</tr>
<tr>
<td>Asymptomatic infection</td>
<td>61 (170)</td>
<td>39 (52)</td>
</tr>
<tr>
<td>A isolate</td>
<td>76 (171)</td>
<td>61 (51)</td>
</tr>
<tr>
<td>Serum antigen detection in tested w:</td>
<td>95 (166)</td>
<td>74.5 (51)</td>
</tr>
<tr>
<td>Meningeal cryptococcosis</td>
<td>100 (96)</td>
<td>89 (19)</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td>97 (146)</td>
<td>86 (29)</td>
</tr>
<tr>
<td>Serum antigen titer in log₂ [95%CI]</td>
<td>9.2 [8.5, 9.9]</td>
<td>6.1 [4.9, 7.3]</td>
</tr>
</tbody>
</table>

**Characteristics in patients with Meningoencephalitis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Positive (n = 170)</th>
<th>Negative (n = 52)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>India ink</td>
<td>88 (156)</td>
<td>52 (31)</td>
<td>&lt; 10⁻³</td>
</tr>
<tr>
<td>CSF cell count/mm³ [IQR]</td>
<td>9 [2, 65]</td>
<td>31 [1, 130]</td>
<td>NS</td>
</tr>
<tr>
<td>CSF protein conc (g/l) [IQR]</td>
<td>0.7 [0.4, 1.2]</td>
<td>0.85 [0.5, 1.1]</td>
<td>NS</td>
</tr>
<tr>
<td>CSF:serum glucose conc.</td>
<td>0.46 [0.42, 0.5]</td>
<td>0.35 [0.27, 0.44]</td>
<td>0.040</td>
</tr>
</tbody>
</table>
Serum CPS +: 83% (40/48) of patients

Extrapulmonary lesions: Ag most often + (p=0.018)

Higher titers if extrapulmonary lesions (p=0.003) or fungemia (p=0.045)

Isolated nodule: Ag less often + (p=0.053)

Lung transplants: less often Ag + (p=0.003)
Antifungal Management Practices and Evolution of Infection in Organ Transplant Recipients with Cryptococcus Neoformans Infection


(Transplantation 2005;80: 1033–1039)

International cohort study of 83 patients

Duration of follow-up of 2.1-5.2 yrs.

Amphotericin B vs. Fluconazole:
- CNS infection (69% vs. 16%, p = 0.00001),
- Disseminated infection (82.7% vs. 20%, p = 0.00001)
- Fungemia (29% vs. 8%, p= 0.046)

M6 survival < if CSF Wk2 culture + (50% vs. 91%, p= 0.06)
Are lipid formulations of AmB better for CNS cryptococcosis in SOT?

Sun et al. CID 2009

Patients with SOT-cryptococcosis treated with polyenes
55 (73.3%) received lipid formulations
20 (26.7%) received AmBd

Overall mortality at 90 d
- 10.9% w AmB lipid formulations
- 40.0% w AmBd

AmB lipid formulations independently associated with a lower mortality (OR, 0.11; 95% CI, 0.02-0.57; P = .008)

Mortality did not differ with or without flucytosine
Optimal therapeutic strategy during cryptococcosis: impact of the Crypto A/D study

8 patients with cryptococcosis: analysis of failure (death or biological failure) at W2 or M3

\( \text{mB + 5FC} = \text{best strategy in case of} \)

- Meningoencephalitis
- High fungal burden
- Neurological abnormalities (26% failure vs. 56% if other strategies, \( p < 0.001 \))
- Thymidine for less than 14 d (OR = 3.30 [1.12-9.70], \( p = 0.030 \))
## Management of cryptococcal meningitis in SOT Patients

**IDSA Guidelines CID 2010**

<table>
<thead>
<tr>
<th>Induction Therapy:</th>
<th>Duration</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>liposomal AmB (3–4 mg/kg per day) or C (5 mg/kg per day) plus flucytosine (100 mg/kg per day)</td>
<td>2 weeks</td>
<td>B-III</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Induction Therapy:</th>
<th>Duration</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>liposomal AmB (6 mg/kg per day) or ABLC (5 mg/kg per day)</td>
<td>4–6 weeks</td>
<td>B-III</td>
</tr>
<tr>
<td>AmB (0.7 mg/kg per day)</td>
<td>4–6 weeks</td>
<td>B-III</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Induction Therapy:</th>
<th>Duration</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluconazole (400–800 mg per day)</td>
<td>8 weeks</td>
<td>B-III</td>
</tr>
<tr>
<td>Fluconazole (200–400 mg per day)</td>
<td>6 months to 1 year</td>
<td>B-III</td>
</tr>
</tbody>
</table>

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1. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate.
2. Immunosuppressive management may require sequential or step-wise reductions.
3. Many transplant recipients have been successfully treated with AmBd; however, issues of renal dysfunction and other side effects are important and the effective dose is imprecise.
Factors associated with mycological failure at W2: Crypto A/D study

Dissemination: OR 2.4 [95%CI, 1.2-4.9] p = 0.015

Serum Ag > 1/512: OR 2.6 [95%CI, 1.3-5.4] p = 0.008

Lack of flucytosine: OR 3.8 [95%CI, 1.9-7.8] p < 0.001 (+++ ≥ 14d)
Independent factors associated with Week 2 mortality: Prospective Crypto A/D Study

Neurological abnormality: 12 vs 3%

Abnormal cerebral imaging: 12 vs. 2%

Abnormal thoracic imaging: 11 vs. 3%

Hyponatremia: 10 vs. 2%
Risk factors for death during SOT-associated cryptococcosis
A study of 111 patients
Singh, Alexander, Lortholary et al. JID 2007

- Use of calcineurin inhibitors: HR = 0.21, p = 0.008

- Renal failure: HR = 3.14, p = 0.037 [only factor found in literature review Husain EID]

90% mortality rate at day 90 (42% in literature review; Husain EID 2001)

- Ring meningitis: vigilance disturbances, lack of headache and liver failure
  Transpl Infect Dis 2002]
Cineurin Inhibitor Agents Interact Synergistically with Antifungal Agents In Vitro against Cryptococcus neoformans Isolates: Correlation with Outcome in Solid Organ Transplant Recipients with Cryptococcosis

<table>
<thead>
<tr>
<th>Type of transplant</th>
<th>2/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td></td>
</tr>
<tr>
<td>Kidney-pancreas</td>
<td>1/4</td>
</tr>
<tr>
<td>Liver</td>
<td>1/4</td>
</tr>
</tbody>
</table>

| Time to onset of *C.neoformans* infection post-transplant, median (range) | 10.5 months (3-29 months) |

<table>
<thead>
<tr>
<th>Immunosuppressive regimen</th>
<th>4/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus, mycophenolate mofetil, prednisone</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Initial sites of involvement</th>
<th>2/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary (any)</td>
<td></td>
</tr>
<tr>
<td>Skin, soft tissue (any)</td>
<td>2/4</td>
</tr>
<tr>
<td>Central nervous system (any)</td>
<td>2/4</td>
</tr>
<tr>
<td>Endocardium (any)</td>
<td></td>
</tr>
</tbody>
</table>

CID 2005
Clinical cases of cryptococcal IRIS during AIDS
Reversal Th2/Th1 and proinflammatory responses and occurrence of cryptococcal IRIS during SOT?
Probability of graft survival in renal transplant recipients with cryptococciosis according to IRIS

Singh, Lortholary et al. Transplantation 2005
Therapeutic recommendations for cryptococcosis-associated IRIS (IDSA Guidelines, CID 2010)

- No need to alter direct antifungal therapy (B-III)
- No specific recommendation for minor IRIS (B-III)
- **Major complications (CNS inflammation)**:
  - Management of raised intracranial pressure
  - Role of steroids (≥ 0.5 mg/kg/d; 2-6 weeks) + antifungal (B-III)
  - NSAIDs/thalidomide? (C-III)
Conclusion

- Cryptococcosis represents 8% of IFI in SOT
- Primary infection/reactivation or graft transmission
- Serum CPS may be negative
- Clinical manifestations and outcome influenced by the immunosuppressive protocol
- IRIS may occur in up to 5% of patients
- AmB lipid formulation as first line therapy if CNS involvement
Thanks
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