Fungal infections in non-neutropenic patients (CL-02)

Chronic Pulmonary Aspergillosis

Department of Molecular Microbiology and Immunology
Nagasaki University Graduate School of Biomedical Sciences

Koichi IZUMIKAWA, M.D., Ph.D.
Chronic forms of Pulmonary Aspergillosis

Definition:
slowly progressive inflammatory pulmonary syndrome due to Aspergillus spp.
Chronic forms of pulmonary aspergillosis

✓ Also Known As;
✓ Chronic cavitary pulmonary aspergillosis (CCPA)
✓ Chronic fibrosing pulmonary aspergillosis (CFPA)
✓ Chronic necrotizing pulmonary aspergillosis (CNPA)
✓ Sub-acute IPA
✓ Semi-invasive pulmonary aspergillosis
✓ Chronic invasive pulmonary aspergillosis
✓ Symptomatic pulmonary aspergilloma
✓ Aspergillus pseudotuberculosis
✓ Complex aspergilloma
✓ Chronic destructive pulmonary aspergillosis
Proposed classification and pathogenesis of chronic pulmonary aspergillosis

Preexisting pulmonary defect, with cavity

Colonization of pulmonary cavity

Aspergillus exposure

Generalized immuno-compromised state (e.g. diabetes, AIDS, alcoholism)

Subtle generalized or pulmonary defense defect

Immune dysregulation

No local generalized defect

Nodular or consolidation, w/ or w/o cavitations:
subacute invasive pulmonary aspergillosis (subacute IPA)
or
chronic necrotizing pulmonary aspergillosis (CNPA)

Multiple cavities w/ surrounding inflammation ±aspergilloma:
chronic cavitary pulmonary aspergillosis (CCPA)
or
complex aspergilloma

Resolution of infection or asymptomatic, stable single aspergilloma:
simple aspergilloma

normal/weak fibrosis response

strong fibrosis response

continuing cavity formations and local inflammation

Extensive pleuro/pulmonary fibrosis:
chronic fibroing pulmonary aspergillosis (CFPA)

Chronic forms of Pulmonary Aspergillosis

Can you tell?
This is
CNPA?
CCPA?
CFPA?
Complex aspergilloma?
Clinical characters of chronic pulmonary aspergillosis (CPA)

Who at risks;

**pre-existing lung diseases;** COPD, Tuberculosis sequelae, bronchiectasis, cystic fibrosis, aspergilloma, post surgery with mild immunocompromising conditions (e.g., HIV infection, leukemia, and chronic granulomatous disease)

Symptoms;

**chronic pulmonary or systemic symptoms (duration, 3 months)**
weight loss, productive cough, or hemoptysis

Images;

**cavitary pulmonary lesion with paracavitary infiltrates, new cavity formation, or expansion of cavity size over time**

Laboratory findings;

serum *Aspergillus* antibody test
isolation of *Aspergillus* spp. from pulmonary or pleural cavity
elevated levels of inflammatory markers

Others;

**Exclusion of other pulmonary pathogens**, by results of appropriate cultures and serological tests
Systemic Mycosis in Japan

Department of Molecular Microbiology and Immunology
Nagasaki University Graduate School of Biomedical Sciences

Year


Total number of Mycosis
Candidiasis
Aspergillosis
Cryptococcosis
Mucor

Reported TB cases
New and relapse cases (per 100,000 population)

France | Germany | Italy | Japan | Netherlands | Portugal | Spain | Sweden | United Kingdom of Great Britain and Northern Ireland | United States of America
---|---|---|---|---|---|---|---|---|---
60 | 50 | 40 | 30 | 30 | 20 | 10 | 10 | 10 | 10


WHO, Communicable Diseases Report
Problems in CPA

**Definition**
→ world-wide consensus required

**Diagnosis**
→ precise and rapid detection tests required
→ development of maker indicating progression

**Treatment**
→ lack of evidence

**Analysis of disease**
→ in vivo model development
Diagnosing CPA

No reliable tests existed yet
Proteomics for discovering new Aspergillus antigen
Ciphergen ProteinChip® System
(SELDI TOF-MS)

Developed for the performing functional analyses such as, expression, interaction, ornamentation or for the refinement/identification of targeted protein

(some images from http://www.ciphergen.co.jp/)
Proteomics for discovering new Aspergillus antigen

Peaks comparison in extracted protein from A. fumigatus MF13 and serum of IPA patient and healthy volunteer

A. fumigatus
MF13

IPA

Healthy

Fungus/
IPA

Fungus/
Healthy

Patient/
Healthy

Department of Molecular Microbiology and Immunology
Nagasaki University Graduate School of Biomedical Sciences
Proteomics for discovering new Aspergillus antigen

Transition of targeted peaks in the course of Legionella and IPA infection case

L. pneumophilla pneumonia

Aspergillus antigen ELISA

Detection of A. fumigatus

Extracted protein from A. fumigatus

Department of Molecular Microbiology and Immunology
Nagasaki University Graduate School of Biomedical Sciences
Proteomics for discovering new Aspergillus antigen

Purification and calibration of targeted peak @ 8560 m/z

Target peak

Department of Molecular Microbiology and Immunology
Nagasaki University Graduate School of Biomedical Sciences
Proteomics for discovering new Aspergillus antigen

Result of PMF and MS/MS analysis

**PMF**
- gi|70993888 Mass: 35178 Score: 71 polyubiquitin (UbiD) [Aspergillus fumigatus Af293]
- gi|55783587 Mass: 34152 Score: 71 polyubiquitin [Aspergillus fumigatus]
- gi|70999548 Mass: 17661 Score: 69 ubiquitin (UbiC) [Aspergillus fumigatus Af293]

**MS/MS**
- gi|70999548 Mass: 17661 Score: 92 ubiquitin (UbiC) [Aspergillus fumigatus Af293]
- gi|55783587 Mass: 34152 Score: 88 polyubiquitin [Aspergillus fumigatus]
- gi|70993888 Mass: 35178 Score: 88 polyubiquitin (UbiD) [Aspergillus fumigatus Af293]
Treatment of CPA

No enough data yet
CPA case
ITCZ oral solution treatment case

[case] 65 Y, Male

[CC] hemosputum, cough


[PI]
1998 : right upper lobectomy (Tbc)
2005~ : cough, hemosputum
2006~ : hemosputum increased
chest CT : fungus ball like shadows in right lower lung.
Platelia EIA: positive, Aspergillus Ab: positive
β-D-gulucan 35.0pg/ml
admission for further treatment

[PE] Height 161cm, Weight 44.3kg, BMI 17.1,
Body temp. 36.8°C, pulse 68/min, regular rhythm
**CPA case**

**ITCZ oral solution treatment**

- 2/16: MCFG 150mg/day
- 2/22: BIPM 0.6g/day
- 3/19: 6 months
- 10/4: BIPM 0.6g/day
- 10/11: VRCZ 200mg/day

**Medications**

- ITCZ 400mg/day
- ITCZ 200mg/day

**Clinical Findings**

- **BALF:** A. fumigatus
- **Sputum:** A. terreus

**Laboratory Values**

- **WBC (/μl):**
  - 8700 6700 5700 5300 6500 8000 7500 7500
- **CRP (mg/dl):**
  - 1.65 5.70 0.19 0.20 0.93 1.46 3.24 0.72
- **β-D-glucan (pg/ml):**
  - 39.5 117.8 90.9 68.2 47.4 25.9 28.9
- **Aspergillus antigen (EIA):**
  - 0.65 0.976 0.985 1.025 0.441 0.461 0.591 0.517

**Department of Molecular Microbiology and Immunology**

Nagasaki University Graduate School of Biomedical Sciences
## CPA treatment
### IDSA GL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNPA</td>
<td>VRCZ</td>
<td>L-AMB</td>
</tr>
<tr>
<td>(Subacute IPA)</td>
<td></td>
<td>ITCZ</td>
</tr>
<tr>
<td></td>
<td>(or)</td>
<td>MCFG</td>
</tr>
<tr>
<td>CCPA</td>
<td>ITCZ</td>
<td>posaconazole</td>
</tr>
<tr>
<td></td>
<td>VRCZ</td>
<td>ABLC</td>
</tr>
<tr>
<td>Aspergilloma</td>
<td>none</td>
<td>caspofungin</td>
</tr>
<tr>
<td></td>
<td>(or)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SURGERY</td>
<td></td>
</tr>
</tbody>
</table>

- Monthly treatment and orally administrative azoles are recommended
- Innateimmune defects demonstrated
- Longterm therapy
- IFN-γ
- The role of medical therapy in treatment of aspergilloma is uncertain

---

NO RCT existed !!
P.O. first and I.V. is optional

Clin Infect Dis 2008; 46:327-360
CPA treatment strategy

① dividing ACUTE and MAINTENANCE phase
ACUTE：IV (single or combination?)
→possibly shorten the admission period
MAINTENANCE：oral AZOLES

② Initiation with oral AZOLES

③ other administrative route of antifungals?
CPA treatment
ongoing clinical trial in Japan

Patients: CPA (CNPA+CCPA), over 100 cases

Antifungals: MCFG i.v. v.s. VRCZ i.v.

The 1st RCT in the world

Multicenter study: 35 institutes in JAPAN
Another route of antifungal administration
nebulized L-AMB & MCFG IPA murine model

**Day-2,0**: Cyclophosphamide 200mg/kg i.p. + Cortisone Acetate 250mg/kg s.c.

**Day0**: MF-13 conidia $1 \times 10^8/ml: 50 \mu l$ intratracheal inoculation

**Day1 ~ 5**: L-AMB 1.2mg/ml : 8ml nebulize once/day

MCFG 1mg/kg/day intraperitoneal

<table>
<thead>
<tr>
<th>Group1: nL-AMB + MCFG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group2: nL-AMB</td>
</tr>
<tr>
<td>Group3: MCFG</td>
</tr>
<tr>
<td>Group4: Control</td>
</tr>
</tbody>
</table>

ICR, ♀, 8weeks

Day-2: Immunosuppression
Day0: Inoculum (i.t.)
Day1 ~ 5: L-AMB inhalation
Another route of antifungal administration

nebulized L-AMB & MCFG IPA murine model
Challenges against CPA

- improve diagnostic rate
- establish the treatment strategy
- evaluate new additional treatment methods

ANALYSIS of CLINICAL FEATURES of CPA
→ development of in vivo model is required
CPA mouse model
Aspergillus biofilm tube intubation

CPA mouse model
Aspergillus biofilm production
CPA mouse model

*A. fumigatus* Biofilm tube intubation + immunosupression
SUMMARY

**Definition**
- world-wide consensus required

**Diagnosis**
- precise and rapid detection tests required
- development of maker indicating progression

**Treatment**
- lack of evidence
- accumulating data about combination therapy

**Analysis of disease**
- in vivo model development
Acknowledgement

Nagasaki University
Shigeru Kohno
Katsunori Yanagihara
Yoshihiro Yamamoto
Hiroshi Kakeya
Masafumi Seki
Taiga Miyazaki
Yoshifumi Imamura
Tomomi Saijo
Takahiro Takazono
Tomo Mihara
Yosuke Nagayoshi

National Institutes of Infectious Diseases
Yoshitsugu Miyazaki
Hideaki Ohno
Satoshi Yamagoe