TB and the rising tide of chronic pulmonary aspergillosis

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Chronic pulmonary aspergillosis

Infection of the lung by *Aspergillus*

Single fungal ball or aspergilloma in a pre-existing cavity
Simple (single) aspergilloma

Patient RK
Haemoptysis, nil else
Positive Aspergillus antibodies in blood
Lobectomy

Wythenshawe Hospital
Simple (single) aspergilloma

Patient NM

August 2006: Community acquired pneumonia requiring ICU care
May 2009:
- Positive Aspergillus antibodies in blood
- New cough
- Lobectomy

Wythenshawe Hospital
Chronic pulmonary aspergillosis

Infection of the lung by *Aspergillus*

- Single fungal ball or aspergilloma in a pre-existing cavity
- Invasive aspergillosis /community acquired infection
- Chronic cavitary pulmonary aspergillosis +/- fungal ball
  - Chronic fibrosing pulmonary aspergillosis +/- fungal ball
'Multicavity' disease is the hallmark of chronic cavitary pulmonary aspergillosis (CCPA)

- Aspergillus IgG antibodies (precipitins)
- Symptoms
<table>
<thead>
<tr>
<th>Condition</th>
<th>Smith</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical tuberculosis</td>
<td>17</td>
</tr>
<tr>
<td>Atypical tuberculosis</td>
<td>16</td>
</tr>
<tr>
<td>ABPA</td>
<td>14</td>
</tr>
<tr>
<td>COPD/emphysema</td>
<td>33</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>17</td>
</tr>
<tr>
<td>Lung cancer survivor</td>
<td>10</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22</td>
</tr>
<tr>
<td>Sarcoidosis (stage II/III)</td>
<td>7</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>14</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>4</td>
</tr>
<tr>
<td>Asthma / SAFS</td>
<td>12</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>4</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
</tbody>
</table>

Smith, unpublished
Frequency of chronic pulmonary aspergillosis after TB

544 patients with proven TB & residual cavities of ≥ 2.5cm diameter

12 months later (n = 544)

- Aspergillus precipitins positive
  - n = 134 (25%)

- Aspergillus precipitins negative
  - n = 410 (75%)

Deaths n = 73
Lost to follow up n = 30
Resection n = 2

Aspergillus precipitins positive
n = 56  n = 16

Aspergillaoma or features consistent with aspergillaoma
n = 78 + 16 = 94 (17%)

No aspergillaoma
n = 56 + 394 = 450 (83%)

Deaths n = 12
Resection n = 5

48 months later (n = 399)

- Aspergillus precipitins positive
  - n = 142 (36%)

- Aspergillus precipitins negative
  - n = 257 (64%)

Aspergillaoma or features consistent with aspergillaoma*
  - n = 56  n = 7
  - n = 88 (22%)

No aspergillaoma
  - n = 311 (78%)

* including resection (n = 7) showing an aspergillaoma
## HRCT during acute tuberculosis with follow up after treatment

<table>
<thead>
<tr>
<th>Findings</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronodules</td>
<td>52 (100)</td>
<td>39 (75)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nodules</td>
<td>46 (88)</td>
<td>29 (56)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mass</td>
<td>22 (42)</td>
<td>4 (8)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tree-in-bud appearance</td>
<td>45 (87)</td>
<td>0 (0)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Consolidation</td>
<td>38 (73)</td>
<td>10 (19)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ground glass opacity</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>0.618</td>
</tr>
<tr>
<td>Cavitation</td>
<td>38 (73)</td>
<td>18 (35)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>15 (29)</td>
<td>23 (44)</td>
<td>0.103</td>
</tr>
<tr>
<td>Fibrotic changes</td>
<td>22 (42)</td>
<td>48 (92)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parenchymal calcification</td>
<td>6 (12)</td>
<td>6 (12)</td>
<td>1.000</td>
</tr>
<tr>
<td>Bullous formation</td>
<td>1 (2)</td>
<td>8 (15)*</td>
<td>0.031</td>
</tr>
<tr>
<td>Lymphadenopathy (&gt;10 mm)</td>
<td>11 (21)</td>
<td>4 (8)</td>
<td>0.092</td>
</tr>
<tr>
<td>Pleural thickening</td>
<td>28 (54)</td>
<td>26 (50)</td>
<td>0.695</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>5 (10)</td>
<td>0 (0)</td>
<td>0.057</td>
</tr>
</tbody>
</table>

* $P < 0.05$; Values in parentheses are percentages.

Lee, Eur J Radiol 2008; 67:100;
Acute tuberculosis

Before treatment: Cavities
After treatment: No cavities

Lee, Eur J Radiol 2008; 67:100;
HRCT during acute tuberculosis with follow up after treatment

Cavities found in 38 (73%) at start of therapy
- multiple in all cases, smooth internal border, with a thick external border

18 (35%) are left with a cavity at end of therapy
- size decreased (disappeared in 20) and cavity wall thin
Tuberculosis and residual cavities post-TB

Many patients with TB are left with a cavity after treatment:

- South african miners: 21%
- Patients in Taiwan: 35% CT
- Patients in Brazil: 30% CT
- Patients in the US: 23%
- Patients in Vietnam: 7%

Lee, Eur J Radiol 2008; 67:100; Sonnenberg et al, Lancet 2001;358:1687
Concordance between radiologists and TB findings on CXRs

<table>
<thead>
<tr>
<th>Finding</th>
<th>Initial radiograph</th>
<th></th>
<th>End of treatment radiograph</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (95% CI)</td>
<td>Specificity (95% CI)</td>
<td>Sensitivity (95% CI)</td>
<td>Specificity (95% CI)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>1.00 (0.95–1.0)</td>
<td>0.50 (0.01–0.99)</td>
<td>0.94 (0.88–0.98)</td>
<td>0.75 (0.35–0.97)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>0.81 (0.64–0.92)</td>
<td>0.93 (0.76–0.99)</td>
<td>0.74 (0.60–0.85)</td>
<td>0.98 (0.88–1.0)</td>
</tr>
<tr>
<td>Cavitary</td>
<td>0.70 (0.47–0.87)</td>
<td>0.86 (0.71–0.95)</td>
<td>0.47* (0.28–0.66)</td>
<td>0.93 (0.84–0.98)</td>
</tr>
</tbody>
</table>

P = 0.013
Key TB assumptions and model construction

1. Assume TB the major underlying disease worldwide - use WHO Global TB database
2. Exclude TB deaths (1 year after starting Rx)
3. Determine only pulmonary TB caseload
4. Assume atypical TB is subsumed within all TB (underestimate in low TB prevalence countries)
Annual attrition after TB

Uzbekistan

### Annual attrition* after TB

<table>
<thead>
<tr>
<th>Country</th>
<th>Rate Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>6.5% annually (1960’s)</td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>15% annually</td>
</tr>
<tr>
<td>Denmark</td>
<td>5% annually</td>
</tr>
<tr>
<td>Guinea Bissau</td>
<td>7%</td>
</tr>
<tr>
<td>South Africa</td>
<td>10% annually (not HIV or MDR TB)</td>
</tr>
<tr>
<td>South Africa</td>
<td>26% annually (HIV+)</td>
</tr>
<tr>
<td>Zambia</td>
<td>7% annually (not HIV or MDR TB)</td>
</tr>
<tr>
<td>South Africa</td>
<td>12% annually (MDR TB)</td>
</tr>
</tbody>
</table>

* alive & remaining undiagnosed among those followed, does not include lost to follow-up, does include cured patients from surgery
Prognosis of chronic pulmonary aspergillosis with an aspergilloma (1956-80)

UK

Jewkes, Thorax 1983;38:572
Prognosis of chronic pulmonary aspergillosis with an aspergilloma (1987)

Cumulative survival (%)

Time from diagnosis of aspergilloma (months)

USA

Tomlinson & Sahn, Chest 1987;92:505
Annual attrition after CPA

Korea

Nam, Int J Infect Dis 2009; epub
Global CPA cases per WHO region related to TB estimate

<table>
<thead>
<tr>
<th>Region</th>
<th>Annual</th>
<th>5 year prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>11,446</td>
<td>42,187</td>
</tr>
<tr>
<td>Americas</td>
<td>12,610</td>
<td>46,475</td>
</tr>
<tr>
<td>Eastern Medit.</td>
<td>20,615</td>
<td>71,398</td>
</tr>
<tr>
<td>Africa</td>
<td>94,602</td>
<td>298,218</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>83,185</td>
<td>299,463</td>
</tr>
<tr>
<td>SE Asia</td>
<td>145,373</td>
<td>503,468</td>
</tr>
<tr>
<td><strong>TOTALS</strong></td>
<td>368,462</td>
<td>1,261,209</td>
</tr>
</tbody>
</table>
Global CPA cases per region related to TB
5 year prevalence estimates

[Map showing global distribution with numbers: 46,475, 42,197, 71,398, 299,463, 298,218, 503,468]
Global CPA cases per region related to TB

Estimate

Cautions:
1) Cavity persistence rate may have changed since 1970 with better regimens
2) Rate of CPA in TB patients without a cavity uncertain
3) Attrition (ie death) rate probably highly variable
4) Assumes almost all TB is neither MDR or XDR
Conclusions

• The incidence and 5 year prevalence of CPA varies widely
• While TB-related CPA is uncommon/rare in western Europe and N. America, it is relatively common in most of the rest of the world
• Other causes of CPA are probably proportionately more common in western Europe and north America
• There are major gaps in our knowledge of the outcomes of TB (other than death) and CPA
• Current treatments other than itraconazole are unaffordable for long term therapy outside the most affluent countries