Tuberculosis and cancer

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Disclosures

- No relevant financial disclosures
- All drugs mentioned have FDA approval for their use.
Question 1

Which of the following does not predispose individuals to TB?

A. Leukemia
B. Hodgkin lymphoma
C. Squamous cell cancer of the tongue
D. Lung cancer
E. Colon cancer
Cancer as a risk factor for TB

- Leukemia, Hodgkin known for a long time
  Clifton EE et al. N Y State J Med 1970;70:274.8
  Arch Environ Health 1970;20:535-6

- Head and neck cancer added later on
Cancer as a risk factor for TB

Retrospective reviews of TB patients diagnosed at two major U.S. cancer centers:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate of TB/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MDACC¹</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>504</td>
</tr>
<tr>
<td>Chronic leukemia</td>
<td>172</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>321</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>178</td>
</tr>
<tr>
<td>Head/neck cancer</td>
<td>155</td>
</tr>
<tr>
<td>Lung</td>
<td>136</td>
</tr>
<tr>
<td>Breast</td>
<td>NA</td>
</tr>
<tr>
<td>Colorectal</td>
<td>NA</td>
</tr>
<tr>
<td>Other solid tumors</td>
<td>50</td>
</tr>
</tbody>
</table>

Cancer as a risk factor for TB

Case-control study in Taiwan (NHI review – 96% of population)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>IRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute leukemia</td>
<td>3.20</td>
<td>0.64-14.87</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3.06</td>
<td>1.37-6.69</td>
</tr>
<tr>
<td>Oral</td>
<td>3.52</td>
<td>1.89-6.51</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>2.18</td>
<td>0.66-6.44</td>
</tr>
<tr>
<td>Esophagus</td>
<td>6.40</td>
<td>1.85-24.88</td>
</tr>
<tr>
<td>Lung</td>
<td>2.81</td>
<td>1.83-4.28</td>
</tr>
<tr>
<td>Other solid tumors</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

True or false: TB is a risk factor for lung cancer.

A. True
B. False
TB as a risk factor for lung cancer

- 2009 meta-analysis
  - 37 case-control and 4 cohort studies

- $RR = 1.74$ [95% CI: 1.48–2.03] controlled for smoking
- $RR = 1.78$ [95% CI: 1.42–2.23] among nonsmokers

- Risk highest 1-5 years after diagnosis
  - $RR 11.14$ [95% CI: 7.57-16.41] in years 1-5
  - $RR 1.99-3.96$ in years 6-10, 11-20, >20

TB as a risk factor for lung cancer

- Case-control study from Taiwan, 1997-2008
  - Used NHI database (same group as before)
  - Controlled for confounders

- HR for cancer in TB group: 1.64 [95% CI: 1.24-2.15]

TB as a risk factor for lung cancer

TB as a risk factor for lung cancer

- Large study of beta-carotene and alpha-tocopherol for lung cancer prevention in Finnish smokers

- Prospective trial

- HR for cancer in those with TB: 1.97 [95% CI: 1.46-2.66]

Prior TB and lung cancer – mortality

- Case review of 3,928 lung cancers in Taiwan

- 31 had TB within 2 years of cancer diagnosis
  - 16 had prior/concurrent TB

- Mortality higher in subjects with prior/concurrent TB than those with no TB or with TB diagnosed after cancer
  - Mostly advanced disease at presentation

Survival from Dx of cancer for subjects with or without prior/concurrent TB

TB, or not TB?

- 68yo homeless man presents with 2-month Hx weight loss, now with dyspnea
  - Long-time smoker
  - Reports staying in a shelter in Atlanta last winter

- CXR reveals right-sided pleural effusion
TB, or not TB?

- Thoracentesis is done
  - Exudative effusion with many lymphocytes
  - Cytology negative for cancer
  - AFB smear and GeneXpert MTB on pleural fluid are neg
  - AFB smear of sputum negative x2

- Pulmonology consulted
  - Can’t do a pleural Bx because pt doesn’t have enough fluid left
  - Recs: No anti-TB therapy, discharge with f/u
Question 3

What do you do?

A. Discharge back to shelter with f/u in clinic

B. Treat empirically for TB

C. Perform more tests

X A.
TB Cases Among Fulton County Residents Reported as Homeless in Previous 12 Months, by Genotype, January 1, 2009–August 17, 2016 (N=146)

Key
- Non-genotyped cases (n=35)
- All genotypes with a single case (n=25)
- All genotypes with 2 cases (n=10)
- All genotypes with ≥3 cases (n=21)
- Outbreak-associated genotype (n=55)

Note: Count incomplete for 2016 at time of analysis
Question 4

What other test would you do?

A. IGRA
B. TST
C. Adenosine deaminase
D. QFT on pleural fluid
E. Combination of the above
F. None of these
Pleural biopsy – the gold standard

- **Histology:** Caseating granulomas
  - Can also get cultures

- **Sensitivity:**
  - Percutaneous: 60-80%
  - Thorascopic: 90-100%


- **Diagnosis when combined with fluid cytology:** 90%

TB, or not TB – IGRAs

- Sensitivity in active TB:
  - TST ~77%
  - QuantiFERON®-TB Gold IT ~70%
  - T-Spot®.TB ~90%
TB, or not TB – why do IGRAs fail?

- Sensitized T-cells may be “compartmentalized” to site of disease
  
  Barnes PF et al.. J Immunol 1989; 142:1114–1119

- Idea: Run the IGRAs on fluid from the site of disease
TB, or not TB – IGRAs on pleural fluid

- 2011 meta-analysis of IGRA test characteristics on TB pleurisy
  - 7 studies included, 213 patients
  - Mostly high-incidence areas (one medium, one low incidence)
  - HIV not reported

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT</td>
<td>63%</td>
<td>75%</td>
<td>92%</td>
<td>75%</td>
</tr>
<tr>
<td>T-Spot</td>
<td>91%</td>
<td>85%</td>
<td>81%</td>
<td>66%</td>
</tr>
</tbody>
</table>

- Significant heterogeneity existed among studies
  - Not possible to conclude that one test is superior

Zhou Q et al. Respirology. 2011 Apr;16(3):473-80
ROC curve – pooled IGRAs performed on pleural fluid (8 studies)

Zhou Q et al. Respirology. 2011 Apr;16(3):473-80
IGRAs on pleural fluid -- Issues

- High rate of indeterminate tests in some studies
  - As high as 52%
  - Both low response and positive control and high background IFN-γ in negative control
    Baba K et al. BMC Infect Dis 2008;8:35

- HIV may make things worse

- T-Spot.TB may be difficult to obtain on pleural fluid

- **Conclusion**: Not ready for prime-time.
TB, or not TB – interferon-γ as a better alternative

- IFN-γ accumulates in pleural fluid of TB patients
- Instead of stimulating cells, just measure IFN-γ directly
TB, or not TB – pleural fluid INF-γ

- 2003 meta-analysis
  - 13 studies
  - 419 patients
  - Threshold values 0.8-13 IU/mL

- Sensitivity: 87% (range 57-100%)
- Specificity: 97% (range 90-100%)

- No effect of HIV in two studies with HIV+ subjects

SROC curve for INF-γ in the diagnosis of pleural TB (all effusions)

SROC curve for INF-γ in the diagnosis of pleural TB with variation in control groups

TB, or not TB – Adenosine deaminase

- Responsible for degrading purines
- Associated with macrocyte maturation
- Accumulates in pleural fluid with TB but not cancer
TB, or not TB – pleural fluid ADA

- 2003 meta-analysis
  - 31 studies
  - 4,738 patients

- Sensitivity: 92% (range 56-100%)
- Specificity: 89% (range 55-100%)

- No effect of HIV in 3 studies with HIV+ subjects
  - Reduced levels in one study with 13 HIV+ subjects

SROC curve for ADA in the diagnosis of pleural TB (all effusions)

SROC curve for ADA in the diagnosis of pleural TB with variation in control groups

TB, or not TB – effect of different pre-test probabilities

<table>
<thead>
<tr>
<th>Pre-test prob</th>
<th>INF-γ</th>
<th></th>
<th>ADA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pos</td>
<td>Neg</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>5%</td>
<td>59%</td>
<td>0.22%</td>
<td>41%</td>
<td>0.4%</td>
</tr>
<tr>
<td>25%</td>
<td>90%</td>
<td>1.2%</td>
<td>81%</td>
<td>2.4%</td>
</tr>
<tr>
<td>85%</td>
<td>99%</td>
<td>17%</td>
<td>99%</td>
<td>24%</td>
</tr>
</tbody>
</table>

TB, or not TB – other sites

- **Peritoneal/pelvic TB**
  - CA-125 elevated and can be used to monitor therapy
  - Unfortunately, it is also elevated in ovarian cancer
    - Can use sex, epi risks, and fluid cytology
    - Laparoscopy may be required
TB, or not TB – other sites

- Can masquerade as mass lesions in many sites

- Biopsy may be necessary
  - Remember to tell them to do cultures!

- Also remember to look for pulmonary TB!
Testicular TB – a sad tale

- Case review of scrotal TB at a hospital in Taiwan, 1995-2005
- 29 cases of scrotal TB found
  - TB initially suspected in only 17%
  - 57% had abnormal CXRs
  - Urine culture/PCR high-yield but performed on a minority
  - 16 underwent orchiectomy prior to Dx

Summary

- Hematologic and head/neck cancers increase susceptibility to TB
- Prior pulmonary TB approximately doubles the risk of subsequent lung cancer
- Pleural TB remains difficult to diagnose, but pleural fluid ADA and INF-γ can assist with diagnosis
- Diagnosis of TB vs cancer in other locations hinges on maintaining a high degree of suspicion for TB