TUBERCULOUS PLEURAL EFFUSION

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CASE 1

- 37 y/o male without significant medical history c/o cough, chest pain, & exertional dyspnea.
- Night sweats & unintentional weight loss.
- No hemoptysis.
- VS: 36.1 C, 58, 18, 106/68, & 96% RA.
- No acute distress.
- Decreased breath sounds noted over the R hemithorax.
- WBC 7.2
CASE 1
CASE 1

- Respiratory Isolation.
- Thoracentesis.
  - WBC 6250 (89% L), RBC 3400
  - pH 7.89, LDH 459, T protein 5.3
  - Glucose 70, Cholesterol 106, TG 3
  - ADA 49 U/L.
  - AFB smear negative.
- PPD positive.
- AFB sputum negative x 3.
- Isoniazid (INH), Rifampin (RIF), Pyrazinamide (PZA), and Ethambutol (EMB) started.
CASE 1

- Pleural and sputum cultures negative at 8 weeks.
- Patient seen in pulmonary clinic 3 months later with mild pleuritic chest pain and minimal exertional dyspnea.
- Completed 6 month course of anti-TB treatment.
- Repeat CT chest.
CASE 2

- 47 y/o male c/o L sided chest pain and progressive dyspnea for 2 weeks.
- Recently (3 months) diagnosed with TB at an outside hospital.
- Unable to accurately describe current medication regimen.
- VS: 36.4 C, 75, 18, 114/74, and 96% RA.
- No acute distress.
- Decreased breath sounds over the L hemithorax.
- WBC 5.2
CASE 2

- Attempted thoracentesis unsuccessful.
- Thoracic surgery evaluation.
- Scheduled for VATS.
- Previous work-up negative AFB sputum, pleural fluid AFB smear negative, closed pleural biopsy culture positive *M. Tuberculosis*.
- Had received 2 months of INH, RIF, PZA, & EMB.
- Decision made to cancel surgery and continue medical management.
- Continues to follow-up with the DOH and is reportedly clinically improved.
CASE 3

- 87 y/o male with a remote history of treated TB
- c/o subjective fever, R-sided chest pain, and progressive dyspnea over the last 4 weeks.
- Recent weight loss.
- No hemoptysis.
- VS: 35 C, 108, 18, 143/69, & 98% RA.
- Ill-appearing male in no acute distress.
- Decreased breath sounds noted over the R hemithorax.
- WBC 7.7
CASE 3
CASE 3
CASE 3

- **Respiratory Isolation**
- **Thoracentesis**
  - WBC 120 (91% L), RBC 4250
  - pH 7.76, LDH 632, T protein 5.1
  - Glucose 91, TG 53
  - ADA > 80 U/L
  - AFB smear/culture negative.
- **Sputum positive for AFB.**
  - PCR (+) *M. tuberculosis*.
- **INH, RFA, PZA, & EMB started.**
INTRODUCTION

- Tuberculosis (TB) has emerged as a global public health epidemic with 9 million new cases and approximately 2 million deaths in 2004.
- The global epidemic of TB has affected the United States (US) where the majority of cases now occur among foreign-born persons.
- In 2005, a total of 14,093 TB cases (4.8 cases per 100,000 population) were reported in the US, representing a 3.8% decline in the rate from 2004.
- Despite decreasing numbers of cases since 1992, TB remains a serious public health problem among certain patient populations and is highly prevalent in many urban areas.


EXTRAPULMONARY TB

- TB can spread to any tissue or organ of the body hematogenously, via the lymphatic system, or by direct extension.
- Common organs involved include the lymph nodes, pleura, bones & joints, brain & meninges, liver & other GI organs, peritoneum, and pericardium.
- Nonpulmonary sites tend to be more common among children and persons with impaired immunity.
- As the incidence of extrapulmonary TB is closely related to the prevalence of TB in an area, the rate varies between countries.
<table>
<thead>
<tr>
<th>Site of Disease</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic</td>
<td>1247</td>
<td>42.0</td>
</tr>
<tr>
<td>Pleural</td>
<td>535</td>
<td>18.0</td>
</tr>
<tr>
<td>Other</td>
<td>354</td>
<td>11.9</td>
</tr>
<tr>
<td>Bone/Joint</td>
<td>329</td>
<td>11.1</td>
</tr>
<tr>
<td>Meningeal</td>
<td>186</td>
<td>6.3</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>164</td>
<td>5.5</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>153</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Total Cases</strong></td>
<td><strong>2968</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

TUBERCULOUS PLEURAL EFFUSION (TPE)

- Classically occurs 3 – 7 months after initial infection with *M. tuberculosis* but may occur at any time during the natural course of the disease.
- Can be a manifestation of primary or reactivation TB.
- Can be seen either isolated or in association with pulmonary TB.
- Complications include tuberculous empyema, pseudochoylothorax, residual pleural thickening, pleural calcification, and thoracic wall infection.
- Solitary and multiple pleural nodules have been reported as unusual manifestations of pleural involvement in TB.
Pleural effusion is one of the most frequent extrapulmonary manifestations of TB.

In the US, the pleura is affected in approximately 4% of all patients with TB with an incidence of 535 cases in 2005.

Historically, a disease of children & young adults although more recent studies report an older mean age.

Men are affected more frequently than women, with ratios of up to 3:1 reported.

Thought to coexist with pulmonary TB in 30 – 50% of cases.

Contradictory data regarding the frequency of tuberculous pleural disease in HIV-positive and HIV-negative patients with TB.
Tuberculous Pleurisy: A Study of 254 Patients

- Retrospective review.
  - Mean age of the patients was 34.1 +/- 18.1 years.
  - 62.2% were < 35 years old.
  - Associated pulmonary lesions were detected in 18.9%.
  - 66.5% were PPD positive.
- Concluded that based on these parameters that tuberculous pleural effusion is a primary form of TB in this region.

The Prevalence of Pulmonary Parenchymal TB in Patients With Tuberculous Pleuritis

- Prospective cohort study.
- South Korea 2004.
  - 106 patients with TB pleuritis.
  - Median age 53 years.
  - Lung parenchymal lesions were noted in 71 patients (67%) on CXR.
    - Using chest CT, 91/106 patients (86%) had parenchymal lesions.
  - Lung parenchymal lesions were more common in this series than has previously been reported.
  - Majority of patients had radiographic findings suggestive of reactivation rather than primary TB.

TB in HIV-Positive Patients in South Africa: A Comparative Radiological Study with HIV-Negative Patients

- 111 patients with active TB.
  - 61 HIV-positive.
  - 50 HIV-negative.
- Adenopathy
  - 50% vs. 8% (p < 0.05)
- Pleural effusions
  - 38% vs. 20% (p < 0.05)
- Cavitation
  - 38% vs. 82% (p < 0.05)
- Atelectasis
  - 31% vs. 82% (p < 0.05)

Radiographic Abnormalities in TB and Risk of Coexisting HIV Infection

- Evaluated chest radiograph abnormalities in 146 patients with new-onset intrathoracic TB (pulmonary, pleural, or hilar/mediastinal adenopathy.
  - 80 patients (55%) were HIV-positive.
  - No significant differences in the incidence of pleural effusions in HIV-positive (33/80; 41%) and HIV-negative (23/66; 35%) patients.
  - Combined data (n = 304, 61% HIV-positive).

Tuberculous Pleurisy Is More Common in AIDS Than in Non-AIDS Patients With TB

  - 2817 cases of TB in non-AIDS patients.
    - 169 (6%) had pleural involvement.
  - 202 cases of TB in patients with AIDS.
    - 22 (11%) had pleural involvement.
- Among all patients with TB in South Carolina, the proportion with pleural involvement was greater in AIDS patients than in non-AIDS patients. (p = 0.01)

Relationship of the Manifestations of TB to CD4 Cell Counts in Patients with HIV Infection.

- 97 HIV-positive patients with tuberculosis in whom CD4 cell counts were available.
- Pleural effusions were noted in 6/58 (10%) of patients with CD4 counts < 200 and 8/29 (28%) of patients with CD4 counts > 200 (p = 0.04).

**ETIOLOGY & PATHOGENESIS**

- A subpleural focus in the lung ruptures into the pleural space 6 – 12 weeks after a primary infection.
  - Mycobacterial antigens enter the pleural space and interact with sensitized T-cells resulting in a delayed hypersensitivity reaction and the accumulation of fluid.
- Hematogenous dissemination and direct extension from a vertebral focus are other routes of entrance to the pleural space.
Mesothelial cells release various chemotactic factors (induced by the presence of *M. tuberculosis*) which regulate the process.

- Neutrophils appear to be the predominant cells in the initial phase.
- Recruitment of monocytes and then lymphocytes.
- After phagocytosing mycobacteria, monocytes act as antigen-presenting cells to the T-lymphocytes which become activated and promote macrophage differentiation & granuloma formation.
CLINICAL PRESENTATION

- Spectrum from an acute illness to an indolent disease.
- Nonproductive cough, pleuritic chest pain, & dyspnea are the most common symptoms.
- Pleural friction rub unusual.
- Fevers are common.
- Leukocytosis is unusual.
- HIV-positive patients often have a more prolonged illness with more severe symptoms & significant physical exam findings.
Pleural effusion is generally unilateral & small to moderate in size.
Massive effusions have been reported in up to 30% of cases.
Bilateral effusions are relatively uncommon & are generally seen in HIV-positive patients.
Can be difficult to determine whether primary or reactivation disease.
Computed Tomography Findings of Tuberculous Pleurisy

- Retrospective review.
- CT scans of 66 patients.
  - Pleural effusion with smooth pleural thickening.
  - Rarely involvement of the mediastinal pleura.
  - Underlying parenchymal lesions were seen in 39%.

**Table 1** Computed tomography findings related to the pleura

<table>
<thead>
<tr>
<th>Pleural effusion</th>
<th>Pleural lesion</th>
<th>Pleural calcification</th>
<th>IIF</th>
<th>IMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>65/66 (98.5%)</td>
<td>37/66 (57.5%)</td>
<td>2/66 (3%)</td>
<td>6/66 (9%)</td>
<td>1/66 (1.5%)</td>
</tr>
</tbody>
</table>

IIF = involvement of interlobar fissure; IMP = involvement of mediastinal pleura.

TUBERCULIN SKIN TESTING

- PPD skin testing may be negative in up to 30% of immunocompetent patients, and in up to 60% of HIV-positive patients.
  - Compartmentalization of CD4+ T-lymphocytes in the pleural space.
  - Suppression of sensitized T-cells in the peripheral circulation & skin by circulating adherent mononuclear cells.
- Almost all immunocompetent patients with an initially negative test will become positive if retested 1 – 2 months later.
PLEURAL FLUID

- Serous or serosanguinous exudate.
- Total protein almost always > 4 g/dL & frequently > 5 g/dL.
- WBC generally < 5000 & predominantly lymphocytes.
- Mesothelial cells < 5% & eosinophils < 10%.
- Low glucose (< 60 mg/dL) & pH (< 7.30) are seen in approximately 20%.
- The glucose is rarely below 20 mg/dl & a pH > 7.40 virtually excludes tuberculous pleurisy.

DIAGNOSIS

- Definitive diagnosis.
  - Demonstration of *M. tuberculosis* in culture of pleural fluid or of tissue obtained at pleural biopsy.

- Presumptive diagnosis.
  - Presence of granulomatous inflammation in histopathology of the pleural biopsy.
DIAGNOSTIC TESTS

- Sputum AFB smear/culture.
- Pleural fluid AFB smear/culture.
- Pleural biopsy culture.
- Pleural biopsy histology.
- The combined use of all tests provides a diagnosis in 82 – 98%.
- Different yields reported in HIV-positive patients.
CONVENTIONAL DIAGNOSIS OF TUBERCULOUS PLEURITIS

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>NUMBER OF CASES</th>
<th>FLUID CULTURE POSITIVE (%)</th>
<th>BIOPSY HISTOLOGY POSITIVE (%)</th>
<th>BIOPSY CULTURE POSITIVE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEIBERT et al.</td>
<td>70</td>
<td>58</td>
<td>84</td>
<td>67</td>
</tr>
<tr>
<td>VALDES et al.</td>
<td>81</td>
<td>38</td>
<td>76.5</td>
<td>56.8</td>
</tr>
<tr>
<td>MOUGDIL et al.</td>
<td>62</td>
<td>54</td>
<td>60</td>
<td>NR</td>
</tr>
<tr>
<td>CHAN et al.</td>
<td>83</td>
<td>23</td>
<td>97</td>
<td>40</td>
</tr>
<tr>
<td>ANTONISKIS et al.</td>
<td>59</td>
<td>77</td>
<td>58</td>
<td>52</td>
</tr>
<tr>
<td>MAERTENS &amp; BATEMAN</td>
<td>62</td>
<td>47</td>
<td>84</td>
<td>71</td>
</tr>
<tr>
<td>KIRSCH et al.</td>
<td>30</td>
<td>NR</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>VALDES et al.</td>
<td>254</td>
<td>36.6</td>
<td>79.8</td>
<td>56.4</td>
</tr>
</tbody>
</table>

Yield of Sputum Induction in The Diagnosis of Pleural TB

- Prospective study.
- 113 patients with pleural effusion.
  - 84 patients diagnosed with pleural TB.
  - 71 HIV-negative & 13 HIV-positive.
  - 64/84 (76%) had no parenchymal opacities identified on CXR.
- Findings suggest that the yield of sputum cultures obtained by induction is high in patients suspected of having pleural TB.

**TABLE 1. YIELD OF DIAGNOSTIC METHODS IN 84 CASES OF TUBERCULOUS PLEURAL EFFUSIONS**

<table>
<thead>
<tr>
<th>Method of Diagnosis</th>
<th>Total</th>
<th>HIV Seronegative (n = 71)</th>
<th>HIV Seropositive (n = 13)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presumptive diagnosis</td>
<td>5 (6)</td>
<td>5 (7)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Pleural biopsy tissue</td>
<td>78 (93)</td>
<td>65 (91)</td>
<td>13 (100)</td>
<td>0.58</td>
</tr>
<tr>
<td>Bacteriologic diagnosis</td>
<td>52 (62)</td>
<td>42 (59)</td>
<td>10 (77)</td>
<td>0.36</td>
</tr>
<tr>
<td>AFB smear positive</td>
<td>14 (17)</td>
<td>9 (13)</td>
<td>5 (38)</td>
<td>0.06</td>
</tr>
<tr>
<td>Culture for M.tb positive</td>
<td>52 (62)</td>
<td>42 (59)</td>
<td>10 (77)</td>
<td>0.36</td>
</tr>
<tr>
<td>Histologic diagnosis</td>
<td>66 (78)</td>
<td>54 (76)</td>
<td>12 (92)</td>
<td>0.28</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>10 (12)</td>
<td>7 (10)</td>
<td>3 (23)</td>
<td>0.18</td>
</tr>
<tr>
<td>AFB smear positive</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>1 (8)</td>
<td>0.28</td>
</tr>
<tr>
<td>Culture for M.tb positive</td>
<td>9 (11)</td>
<td>7 (10)</td>
<td>2 (15)</td>
<td>0.62</td>
</tr>
<tr>
<td>Sputum induction</td>
<td>44 (52)</td>
<td>34 (48)</td>
<td>10 (77)</td>
<td>0.10</td>
</tr>
<tr>
<td>AFB smear positive</td>
<td>10 (12)</td>
<td>7 (10)</td>
<td>3 (23)</td>
<td>0.18</td>
</tr>
<tr>
<td>Culture for M.tb positive</td>
<td>44 (52)</td>
<td>34 (48)</td>
<td>10 (77)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: AFB = acid fast bacilli; M.tb = Mycobacterium tuberculosis.

* p Value of the yield of diagnostic methods between HIV seronegative and HIV seropositive tuberculous pleural patients.

n = number of cases (96).

“Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests.”
NEWER DIAGNOSTIC PARAMETERS

- Adenosine Deaminase
- Interferon gamma
- Lysozyme
- PCR
- Radiometric mycobacterial culture (BACTEC)
- Antimycobacterial antibodies
- Tuberculostearic acid
- SC5b-9
- Immunosuppressive Acidic Protein
- IL-2, IL-6, IL-12, IL-18.
- Leptin
ADENOSINE DEAMINASE (ADA)

- Enzyme that catalyzes the conversion of adenosine & deoxyadenosine to inosine & deoxyinosine.
- 3 principal molecular forms known as ADA1, ADA1+CP, and ADA2.
  - ADA1 isoenzyme is found in all cells.
  - ADA2 isoenzyme is present mainly in monocytes and macrophages.
- Numerous studies have demonstrated elevated ADA levels in tuberculous pleural effusions.
  - Elevated levels are largely due to increased ADA2.
ADENOSINE DEAMINASE (ADA)

- Elevated levels of ADA are also seen in pleural effusions due to lymphoma, adenocarcinomas, rheumatoid pleuritis, SLE, and empyemas.
- For the diagnosis of TPE, various reports have quoted a wide range of cut-off values from 40 to 80 U/L.
- Some debate regarding the notion that ADA levels are significantly different in HIV-positive patients with TPE compared to patients who are HIV-negative.
ADA Activity in Pleural Effusions: An Aid to Differential Diagnosis.

- ADA concentrations were measured in effusions from 96 patients.
  - Tuberculous pleurisy (21 cases), mean ADA 83.04 IU/L.
  - Metapneumonic pleurisy (15 cases), mean ADA 17.26 IU/L.
  - Pleuropulmonary malignancies (18 cases), mean ADA 15.54 IU/L.
  - Cirrhosis/Ascites (25 cases), mean ADA 4.06 IU/L.
  - Abdominal malignancies (17 cases), mean ADA 11.46 IU/L.
- Variance analysis of the 5 groups showed a highly significant difference (p < 0.001).
- Concluded that the ADA assay seemed to be a simple clinical test in the differential diagnosis of exudative pleurisy.


- ADA activity in 218 patients with exudative pleural effusion.
  - Divided by final diagnosis: (1) TB, 82 patients; (2) malignancy, 98 patients; (3) parapneumonic effusions, 14 patients; (4) miscellaneous, 14 patients; & (5) idiopathic, 10 patients.
  - The mean ADA level for tuberculous effusions was 123.25 IU/L & 30.36 IU/L for nontuberculous effusions.
  - Using 70 IU/L as a cut-off value the ADA test exhibited a sensitivity of 98% and a specificity of 96% for the diagnosis of pleural TB.
  - A review of the literature (2,251 patients) showed a combined sensitivity of 99% and a specificity of 89%.

Determination of ADA Activity and its Isoenzymes for Diagnosis of Pleural Effusions

- 87 patients with pleural effusion.
- Divided into four groups: (1) transudates, 16 patients; (2) parapneumonic, 10 patients; (3) malignant, 25 patients; and (4) tuberculous, 36 patients.
- Using a cut-off value for ADA of 47 U/L the sensitivity was 91% and the specificity was 89%.
- Using a cut-off value for ADA2 of 29 U/L the sensitivity was 93% and the specificity was 92%.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Pleural fluid and serum total adenosine deaminase (ADA), ADA₁ and ADA₂ activities and diagnostic values between the tuberculous and non-tuberculous group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADA (U/L)</td>
</tr>
<tr>
<td>Tuberculous group</td>
<td>85.2±28.7</td>
</tr>
<tr>
<td>Non-tuberculous group</td>
<td>52.8±18.1*</td>
</tr>
<tr>
<td>Cut-off value (U/L)</td>
<td>47</td>
</tr>
<tr>
<td>Sensitivity%</td>
<td>91</td>
</tr>
<tr>
<td>Specificity%</td>
<td>89</td>
</tr>
<tr>
<td>PPV%</td>
<td>82</td>
</tr>
<tr>
<td>DA%</td>
<td>89</td>
</tr>
</tbody>
</table>

* P<0.05; ** P<0.001 with respect to the tuberculous pleurisy group. PPV, positive predictive value; DA, diagnostic accuracy.

Diagnostic Value of Pleural Fluid Adenosine Deaminase in Tuberculous Pleuritis with Reference to HIV Coinfection and a Bayesian Analysis

- 216 patients with pleural effusion.
- Using a cut-off value for ADA of 60 U/L the sensitivity was 95% and the specificity was 96% for diagnosing TB pleuritis.
- The mean ADA level was 110 U/L in 37 HIV-positive patients with tuberculous pleural effusion and 114 U/L in 52 HIV-negative patients with tuberculous pleural effusion.

Diagnostic Value of Pleural Fluid Adenosine Deaminase in Tuberculous Pleuritis with Reference to HIV Coinfection and a Bayesian Analysis

INTERFERON GAMMA

- Lymphokine produced by T-lymphocytes in response to antigen stimulation.
- Enhances macrophage phagocytic activity against Mycobacteria.
- Pleural fluid levels are increased in tuberculous pleural effusion compared with other exudative effusions.
- False-positive results have been described in parapneumonic effusions, lymphomas, and other malignant effusions.
80 inpatients with pleural effusion.

Divided into 5 groups:
- Tuberculous pleural effusions (30)
- Malignancy (20)
- Idiopathic (10)
- Parapneumonic (10)
- Transudates (10)

The mean interferon gamma level in patients with tuberculous pleural effusions was 91.2 U/L and in all the other groups it was < 2 U/L.

Interferon Gamma in 388 Immunocompromised and Immunocompetent Patients for Diagnosing Pleural TB.

- 388 patients with pleural effusion.
  - Using a cut-off value of 3.7 U/mL the sensitivity was 99% and the specificity was 98% for diagnosing tuberculous pleural effusion.
  - 9/73 patients with tuberculous pleural effusion were HIV-positive.
  - There was no statistically significant difference in HIV-positive and HIV-negative patients.

66 patients with lymphocytic exudative pleural effusions.
- Tuberculous (39 patients).
  - Mean concentration of interferon gamma was 1493.3 pg/mL.
- Nontuberculous (27 patients.)
  - Mean concentration of interferon gamma was 80.1 pg/mL.
- Using a cut-off point of 240 pg/mL the sensitivity was 94.9% and the specificity was 96.3% for diagnosing tuberculous pleural effusions.
- No significant difference in the values between HIV-positive and HIV-negative patients.

LYSOZYME

- Enzyme present in the epithelioid cells of granulomas, activated macrophages, and certain tumor cells.
- Frequently higher in tuberculous pleural effusion compared to other exudative effusions.
- Elevated levels can also be seen in parapneumonic effusions, empyemas, malignancies, post-thoracic surgery, CVD, CHF, and pleural sarcoidosis.
Pleural Fluid Lysozyme In Tuberculous and Non-Tuberculous Pleurisy

- 37 patients with pleural effusion.
- Lysozyme concentrations in both plasma and pleural fluid were significantly higher in patients with tuberculous pleurisy than in those with non-tuberculous pleurisy.
- Pleural fluid concentration of lysozyme in patients with TB was significantly higher than the plasma concentration.

Mean (± SD) lysozyme concentrations (mg/l) in plasma and pleural fluid of patients with tuberculous and non-tuberculous pleurisy

<table>
<thead>
<tr>
<th>Group</th>
<th>Plasma</th>
<th>Pleural fluid</th>
<th>Pleural fluid:plasma ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculous pleurisy (n = 12)</td>
<td>12.7 ± 5.0</td>
<td>237 ± 8.7</td>
<td>1.99 ± 0.7 *P&lt;0.001</td>
</tr>
<tr>
<td>Non-tuberculous pleurisy (n = 22)</td>
<td>9.3 ± 3.2</td>
<td>8.3 ± 3.1</td>
<td>0.89 ± 0.2 *P&lt;0.001</td>
</tr>
<tr>
<td>Bacterial empyema (n = 3)</td>
<td>13.5 ± 5.7</td>
<td>371.6 ± 47.5</td>
<td>29.0 ± 9.7</td>
</tr>
</tbody>
</table>

*Student’s t test.

Meaning and Diagnostic Value of Determining the Lysozyme Level of Pleural Fluid.

- 141 patients with pleural effusions.
  - TB (54)
  - Malignancy (35)
  - Transudates (12)
  - Parapneumonic (6)
  - Empyema (8)
  - Miscellaneous (6)
  - Idiopathic (20)

- Excluding patients with empyemas, a PL/SL ratio of 1.2 showed a sensitivity of 100% and a specificity of 94.9% for the diagnosis of tuberculous pleural effusion.

POLYMERASE CHAIN REACTION (PCR)

- Based on the amplification of a specific genomic sequence of *M. tuberculosis*.
- Provides a rapid diagnosis.
- Can identify the type of mycobacteria.
- May be useful for determining drug susceptibility.
- Variable sensitivities reported.
- Theoretically highly specific.
- Expensive.
Rapid Diagnosis of Pleural TB By PCR

- 107 patients with pleural effusion.
  - 21 patients with pleural TB.
  - PCR assay based on detecting a 123-bp DNA segment beginning to the insertion sequence IS6110, specific of *M. tuberculosis* complex.
  - Sensitivity 81%.
  - Specificity 98%.
  - All culture-positive specimens were PCR positive.

PCR for the Diagnosis of Pleural TB in Immunocompromised and Immunocompetent Patients

- 131 patients with pleural effusion.
  - 33 patients with pleural TB.
  - Sensitivity 42%.
  - Specificity 99%.
- No statistically significant differences found with respect to HIV status.

### Table 2. Sensitivity of PCR under different conditions for diagnosing pleural tuberculosis in 33 patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacterial culture of pleural fluid (no.)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (13)</td>
<td>0.77 (0.46–0.95)</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Negative (20)</td>
<td>0.20 (0.06–0.44)</td>
<td></td>
</tr>
<tr>
<td>Diagnostic group (no.)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (20)</td>
<td>0.55 (0.32–0.77)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Group B (12)</td>
<td>0.17 (0.02–0.48)</td>
<td></td>
</tr>
<tr>
<td>HIV serology (no.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (18)</td>
<td>0.33 (0.13–0.59)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive (7)</td>
<td>0.43 (0.10–0.82)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: The overall sensitivity (95% CI) of PCR was 0.42 (0.25–0.61).

NS = not significant.
* Fisher's exact test was used for comparisons.
† Mycobacterial culture of the pleural fluid sample on which PCR was performed.
‡ Based on diagnostic criteria for tuberculosis.

Evaluation of PCR, ADA, and Interferon Gamma in Pleural Fluid for the Differential Diagnosis of Pleural TB

- 140 patients with pleural effusion (42 confirmed pleural TB, 19 probable pleural TB, 70 nontuberculous etiology, and 9 idiopathic).
  - PCR (73.8% & 90%)
  - ADA (88% & 85.7%)
  - IFN-gamma (85.7% & 97.1%)
- Positive & negative predictive values were maintained over a wide range of prevalences of pleural TB.
  - IFN-gamma had the highest PPV (94.7%)
  - ADA had the highest NPV (88.2%)

NEWER DIAGNOSTIC PARAMETERS

- **ADA**
  - Well-studied.
  - Optimal cut-off value unclear.

- **Interferon gamma**
  - Higher cost and slowness in obtaining results have limited its use.

- **Lysozyme**
  - PL/SL probably more sensitive than PL alone.

- **PCR**
  - Promising technique.
  - Wide range of reported sensitivities.
  - Expensive.
The basic principles that underlie the treatment of pulmonary TB also apply to extrapulmonary forms of the disease.

Generally, the mycobacterial burden with tuberculous pleural effusion is low and spontaneous resolution within 2 – 4 months is common.

It has been reported that up to 65% of untreated patients with pleural TB develop pulmonary TB within 5 years.
TREATMENT OF TUBERCULOUS PLEURAL EFFUSION

- INH, RIF, PZA, and EMB for 2 months followed by INH and RIF for an additional 4 months.
- Corticosteroids not recommended.
- Pleural space drainage.

<table>
<thead>
<tr>
<th>Site</th>
<th>Length of therapy (mo)</th>
<th>Rating (duration)</th>
<th>Corticosteroids†</th>
<th>Rating (corticosteroids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node</td>
<td>6</td>
<td>A1</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>6–9</td>
<td>A1</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Pleural disease</td>
<td>6</td>
<td>AII</td>
<td>Not recommended</td>
<td>D1</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>6</td>
<td>AII</td>
<td>Strongly recommended</td>
<td>AI</td>
</tr>
<tr>
<td>CNS tuberculosis including meningitis</td>
<td>9–12</td>
<td>BII</td>
<td>Strongly recommended</td>
<td>AI</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>6</td>
<td>AII</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>6</td>
<td>AII</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>6</td>
<td>AII</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
</tbody>
</table>

* For rating system, see Table 1.
† Duration of therapy for extrapulmonary tuberculosis caused by drug-resistant organisms is not known.
‡ Corticosteroid preparations vary among studies. See Section 8.3 for specific recommendations.

Centers for Disease Control and Prevention. Treatment of Tuberculosis. ATS, CDC, and IDSA. MMWR 2003;52
TREATMENT OF TUBERCULOUS PLEURAL EFFUSION

- With therapy, most patients become afebrile within 2 weeks, and pleural fluid is usually resorbed within 6 weeks.
- During the initial phase of treatment, some patients may show an increase in pleural effusion.
- Treatment is essentially the same in patients with HIV infection as for patients who are HIV-negative.
  - Higher rates of drug resistance.
  - Some experts suggest the routine use of 9 – 12 month regimens.
  - Prolonged treatment is suggested if clinical or bacteriological response is slow or less than optimal.
Adjunctive corticosteroids have been proposed in the treatment of tuberculous pleural effusion to reduce the associated inflammation and fibrosis.

May accelerate the resolution of clinical symptoms and the reabsorption of pleural fluid.

Some concerns regarding suppression of the immune response and worsening of the infection, especially in patients who are HIV-positive.
STEROIDS FOR TREATING TUBERCULOUS PLEURISY

- Meta-analysis of randomized trials evaluating the effects of adjunctive corticosteroids in patients diagnosed with TB pleurisy.
  - 3 small trials (n = 236)
  - Insufficient power to examine death as an outcome.
  - No difference in residual lung function between steroid and control groups at completion of treatment.
  - Secondary outcomes trended towards benefit with steroids rather than harm, but none were statistically significant.
  - Adverse effects were few and did not result in treatment discontinuation.
  - Overall conclusion was that there is insufficient evidence to know whether steroids are effective in the treatment of tuberculous effusion.

Pigtail Drainage In The Treatment of Tuberculous Pleural Effusions: A Randomized Study

- 61 patients with TPE were randomized into 2 groups.
  - 30 patients received pigtail drainage combined with anti-TB drugs.
  - 31 patients received only anti-TB drugs.
- Found that the addition of pigtail drainage to an effective anti-TB regimen has minimal clinical relevance and does not reduce the level of RPT.


**Table 2** Outcome of pigtail drainage in patients with tuberculous pleurisy

<table>
<thead>
<tr>
<th></th>
<th>Drainage group (n=30)</th>
<th>No drainage group (n=31)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) days of fever</td>
<td>0 (0–6)</td>
<td>0 (0–5)</td>
<td>0.769*</td>
</tr>
<tr>
<td>Median (IQR) days of dyspnoea</td>
<td>4 (4–5)</td>
<td>8 (7–16)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Pleural thickening &gt;2 mm (%)</td>
<td>16 (53)</td>
<td>16 (51)</td>
<td>0.893†</td>
</tr>
<tr>
<td>Pleural thickening &gt;10 mm (%)</td>
<td>8 (26)</td>
<td>8 (25)</td>
<td>0.939†</td>
</tr>
<tr>
<td>Median (IQR) FVC % predicted</td>
<td>85.5 (69–94)</td>
<td>88 (78–96)</td>
<td>0.568*</td>
</tr>
</tbody>
</table>

IQR=interquartile range; FVC=forced vital capacity.
*Mann-Whitney U test. †χ² test
RESIDUAL PLEURAL THICKENING (RPT)

- Most frequent complication.
- Incidence varies according to the time of evaluation and degree of thickness reported.
- Unclear why some patients develop it.
- Thought that neither patient clinical characteristics nor pleural fluid biochemistry are predictive of its development.
- Usually considered to have minimal impact of lung function.
Are Pleural Fluid Parameters Related to the Development of RPT in TB?

- Retrospective review.
- 56 patients.
  - 24 RPT > 2 mm.
  - 11 RPT > 10 mm.
- Development of RPT >10 mm.
  - Higher levels of lysozyme & TNF.
  - Lower pH.
  - Lower glucose levels.

Table 3—Pleural Fluid Characteristics (RPT ≥10 mm)*

<table>
<thead>
<tr>
<th></th>
<th>RPT Present (n=11)</th>
<th>RPT Absent (n=45)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH, U/L</td>
<td>627.7</td>
<td>410.8</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>51</td>
<td>73.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Proteins, g/L</td>
<td>5.01</td>
<td>5.07</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>7.20</td>
<td>7.30</td>
<td>0.02</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>82.7</td>
<td>88.5</td>
<td>NS</td>
</tr>
<tr>
<td>Amylase, U/L</td>
<td>96.2</td>
<td>111.6</td>
<td>NS</td>
</tr>
<tr>
<td>Cells, μL</td>
<td>4.467</td>
<td>3.606</td>
<td>NS</td>
</tr>
<tr>
<td>ADA, U/L</td>
<td>74.1</td>
<td>87.3</td>
<td>NS</td>
</tr>
<tr>
<td>IFN-γ, U/mL</td>
<td>91.7</td>
<td>87</td>
<td>NS</td>
</tr>
<tr>
<td>Lysozyme, ng/mL</td>
<td>26.4</td>
<td>16.7</td>
<td>0.01</td>
</tr>
<tr>
<td>TNF-α, ng/mL</td>
<td>577.2</td>
<td>275.5</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Mean concentrations of pleural fluid biochemical components and markers in patients separated by presence or absence of RPT ≥10 mm.

Functional Sequelae of Tuberculous Pleurisy in Patients Correctly Treated

- 81 patients treated for tuberculous pleurisy.
  - PFTs & CXRs done at admission, at discharge, and at the end of follow-up.
  - 8/81 patients had a restrictive ventilatory defect.
    - PF showed lower LDH and higher cholesterol, TG, & % lymphocytes.
  - Weak correlation was found between the FVC and the degree of radiographic pleural thickening at the end of follow-up ($r = -0.298; p < 0.01$).
  - The sensitivity of RPT > 2 mm for a restrictive FS was 50%, with a specificity of 64%. Selecting 10 mm as a cut-off point, the sensitivity would be 25% with a specificity of 96%.

| Table 1—Changes in Pulmonary Function With Treatment* |
|-----------------|-----------------|-----------------|
| Variables       | Hospital Admission | Hospital Discharge | End of Follow-up |
| FVC, %          | 60 ± 21 (21)     | 72 ± 16 (61)     | 97.6 ± 17 (81)   |
| FEV₁/FVC, %     | 103 ± 12 (21)    | 103 ± 11 (61)    | 105 ± 9 (81)     |
| TLC, %          | 71.4 ± 16 (12)   | 79.6 ± 14 (24)   | 95.4 ± 15 (81)   |

*Values given as mean ± SD (No. of patients).
Resolution of Residual Pleural Disease According to Time Course in Tuberculous Pleurisy During and After the Termination of Antituberculosis Medication

- Chest radiographs of 85 patients with tuberculous pleurisy were followed prospectively from diagnosis to 24 months after the start of medication.
  - No significant relationship was found between RPO at 24 months and the initial PO size.
  - RPO > 10 mm at 24 months was only correlated with initial pleural fluid loculation and was not correlated with any other PF parameters.
  - 49/85 patients showed further resolution of RPO after 6 months of therapy.
    - Associated with significantly higher levels of initial ESR and PF LDH but not with initial PO size.

SUMMARY

- Pleural TB is one of the most frequent extrapulmonary manifestations of TB.
- TB should be considered a diagnostic possibility in any patient with an exudative effusion.
- Definitive diagnosis requires the identification of *M. tuberculosis* in the pleural fluid or biopsy.
- Alternative diagnostic methods may eventually obviate the need for biopsy.
- Without treatment, TPE is often self-limited but up to 65% of patients may develop TB in the following 5 years.
- Treatment is essentially the same as for pulmonary TB.
- RPT is the most frequent complication but often does not cause a clinically significant restrictive ventilatory defect.
- Significant resolution of RPT may be seen up to 1 year after the initiation of treatment.