APPROACH TO THE PATIENT WITH A PLEURAL EFFUSION OF UNCLEAR ETIOLOGY

STÉPHANE BEAUDDOIN MD, FRCP(C)
RESPIROLOGIST, MCGILL UNIVERSITY HEALTH CENTER
CONFLICTS DISCLOSURES

• I have received yearly educational grants (in-kind equipment) from Olympus Inc. for bronchoscopy simulation seminars

• I get remunerated for performing medical thoracoscopy, but not for imagery or surgical-based techniques
LEARNING OBJECTIVES

• 1. Recognize that a high percentage of pleural effusion diagnoses are unclear after initial assessment

• 2. Describe the approach, diagnosis and investigation for a pleural effusion of unknown cause

• 3. Define the role of imagery and/or pleural biopsy in the setting of pleural effusion of unknown cause
MR D 86 YEARS-OLD MALE WITH A STERILE LYMPHOCYTIC PLEURAL EXUDATE

- **PMHx:** HTN, A fib, BPH, heart murmur
- **Rx:** ASA, furosemide, ramipril, tamsulosin
- Born in Romania
- Non-smoker
- Retired engineer
MR D 86 YEARS-OLD MALE WITH A STERILE LYMPHOCYTIC PLEURAL EXUDATE

- Is this a true exudate?
- What is the differential diagnosis?
- What is the meaning of a negative cytology?
  - Should we repeat the thoracentesis?
- What is the role of CT scan?
  - What kind of CT scan to get?
- Should we do a PET scan?
- What about biomarkers?
- Should a pleural biopsy be done?
  - If so, what kind?
INTRODUCTION

• Pleural effusions are common

• Pleural effusions can cause symptoms that require palliation

• The differential diagnosis of a pleural effusion is remarkably wide
**A DAUNTING DIFFERENTIAL DIAGNOSIS TO DEAL WITH**

<table>
<thead>
<tr>
<th>Transudate</th>
<th>Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Infections</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Systemic inflammatory disorders</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Occupational</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Urinothorax</td>
<td>Trauma</td>
</tr>
<tr>
<td>CSF leak</td>
<td>Drugs</td>
</tr>
<tr>
<td>SVC syndrome</td>
<td>Intra-abdominal processes</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous causes</td>
</tr>
</tbody>
</table>
APPROACH TO THE UNDIAGNOSED EFFUSION: THE BASICS

• Review of drug history

• Review of system for inflammatory disorders, trauma, infectious symptoms, and venous thromboembolism

• Thorough occupational history with a particular attention to asbestos exposure
AUDIENCE PARTICPATION REQUIRED!

- Online
  - PollEv.com/cheatmd

- By text message
  - Text chestmd to 37607 to join
  - Then text your answer for each question

Please keep your phones on silent mode!
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help or Open poll in your web browser
APPROACH TO THE UNDIAGNOSED EFFUSION: THE WBC DIFFERENTIAL

• Lymphocytic profile ≥ 50% of WBC
  • Malignancy
  • TB
  • Rheumatoid arthritis
  • Late post-CABG effusion
  • CHF and many other reactive effusions

• Neutrophilic profile
  • Parapneumonic effusion or effusion related to an abdominal infection
  • Pulmonary embolism

• Eosinophilic profile ≥ 10% of WBC
  • Recent pneumothorax or pleural bleeding
  • Pulmonary embolism
  • Certain drugs
  • Eosinophilic pneumonia
  • Churg-Strauss
  • Parasitic infections
  • TB, benign asbestos effusion
  • Malignancy
APPROACH TO THE UNDIAGNOSED EFFUSION: PLEURAL ACIDOSIS

- Differential diagnosis of an effusion with a severely reduced pH < 7.2 and/or glucose < 3.4 mmol/L
  - Parapneumonic effusion and empyema
  - Malignancy of any origin
  - TB
  - Rheumatoid arthritis
  - Hemothorax
  - Eosophageal rupture
  - Urinothorax
  - Paragonimiasis and Churg-Strauss
TAKE HOME MESSAGE

• Because the differential diagnosis is wide and the basic fluid analyses non-specific, a systematic approach to pleural effusions is necessary

  • It should include a thorough occupational history with an in-depth search for asbestos exposure

• In the absence of long-standing RA, a lymphocytic effusion with a low pH and / or glucose is caused by malignancy or TB until proven otherwise
TB & PLEURAL EFFUSIONS

- Tuberculous pleurisy
  - Subacute presentation
  - Not contagious unless parenchymal disease is present
  - Pleural fluid:
    - Prominent lymphocytosis, low pH, low glucose, little to no mesothelial cells
    - AFB smear rarely +
    - Cx + in < 30% of cases in non-HIV pts
  - Does not require drainage unless causing dyspnea

- Tuberculous empyema and bronchopleural fistula
  - Acute presentation usually in association with cavitary disease with frank pus +/- hydropneumothorax
  - Requires aggressive pleural drainage like an empyema
MR D 86 YEARS-OLD MALE WITH A STERILE LYMPHOcytIC PLEURAL EXUDATE

- **PMHx**: HTN, A fib, BPH, heart murmur

- **Rx**: ASA, furosemide, ramipril, tamsulosin

- Born in Romania

- Non-smoker

- Retired engineer
MR D 86 YEARS-OLD MALE WITH A STERILE LYMPHOCYTIC PLEURAL EXUDATE

- Pleural fluid analyses:
  - 60% lymphocytes
  - Unrevealing microbiology
  - LDH 230/180
  - Protein 35/66
  - Glucose 6.2
  - pH 7.34

Benign cytology
## A Daunting Differential Diagnosis to Deal With

<table>
<thead>
<tr>
<th>Transudate</th>
<th>Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Infections</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Systemic inflammatory disorders</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Occupational</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Urinothorax</td>
<td>Trauma</td>
</tr>
<tr>
<td>CSF leak</td>
<td>Drugs</td>
</tr>
<tr>
<td>SVC syndrome</td>
<td>Intra-abdominal processes</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous causes</td>
</tr>
</tbody>
</table>
IS THIS A TRUE EXUDATE?
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help
or
Open poll in your web browser
LIMITATIONS OF PLEURAL FLUID ANALYSES

Table 1. Diagnostic Accuracy for Most Useful Findings for Diagnosis of Pleural Exudate

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>Positive LR (95% CI)</th>
<th>I², %</th>
<th>Negative LR (95% CI)</th>
<th>I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural cholesterol &gt;55 mg/dL⁵,⁷,⁷⁷, rangeᵇ</td>
<td>379</td>
<td>85-94ᵇ</td>
<td>95-99ᵇ</td>
<td>7.1-250ᵇ</td>
<td></td>
<td>0.07-0.16ᵇ</td>
<td></td>
</tr>
<tr>
<td>Pleural LDH&gt;200 U/L²,⁵,⁶⁶</td>
<td>439</td>
<td>70 (64-75)</td>
<td>98 (93-100)</td>
<td>18 (6.8-46)</td>
<td>0</td>
<td>0.32 (0.27-0.38)</td>
<td>0</td>
</tr>
<tr>
<td>Pleural:serum cholesterol ratio &gt;0.3³,⁴,⁵,⁷⁷</td>
<td>496</td>
<td>93 (90-96)</td>
<td>94 (90-97)</td>
<td>14 (5.5-38)</td>
<td>67</td>
<td>0.08 (0.05-0.12)</td>
<td>0</td>
</tr>
<tr>
<td>Pleural:serum LDH ratio &gt;0.6²,⁵,⁶,⁶⁶,⁷⁷,⁸¹</td>
<td>736</td>
<td>88 (84-91)</td>
<td>91 (88-94)</td>
<td>9.2 (5.9-14)</td>
<td>22</td>
<td>0.14 (0.10-0.20)</td>
<td>29</td>
</tr>
<tr>
<td>Pleural:serum protein ratio &gt;0.5²,⁵,⁶,⁶⁶,⁷⁷,⁸¹</td>
<td>753</td>
<td>90 (87-93)</td>
<td>90 (86-93)</td>
<td>7.0 (2.7-18)</td>
<td>86</td>
<td>0.12 (0.09-0.16)</td>
<td>0</td>
</tr>
<tr>
<td>Combined, ≥1 of Light’s criteria³,⁴,⁵,⁷²,⁷⁵,⁷⁷</td>
<td>738</td>
<td>97 (95-98)</td>
<td>85 (81-89)</td>
<td>5.2 (3.3-8.5)</td>
<td>68</td>
<td>0.04 (0.02-0.11)</td>
<td>47</td>
</tr>
<tr>
<td>Pleural protein &gt;3 g/dL²,⁵³,⁵⁷,⁶⁶</td>
<td>270</td>
<td>88 (82-92)</td>
<td>86 (76-93)</td>
<td>5.1 (2.5-11)</td>
<td>37</td>
<td>0.14 (0.07-0.32)</td>
<td>67</td>
</tr>
<tr>
<td>Pleural LDH&gt;2/3 upper limit of normal⁶⁸,⁷⁷</td>
<td>207</td>
<td>88-89ᵇ</td>
<td>93-100ᵇ</td>
<td>1.7-13ᵇ</td>
<td></td>
<td>0.23-0.26ᵇ</td>
<td></td>
</tr>
<tr>
<td>Serum:pleural albumin gradient &lt;1.2 mg/dL⁷²,⁷⁴</td>
<td>145</td>
<td>86-95ᵇ</td>
<td>42-100ᵇ</td>
<td>1.5-36ᵇ</td>
<td></td>
<td>0.06-0.32ᵇ</td>
<td></td>
</tr>
</tbody>
</table>

Wilcox ME et al. JAMA RCE series 2014
THE GENESIS

<table>
<thead>
<tr>
<th>PF Test</th>
<th>Meta-analysis ROC Cutoff Point</th>
<th>Previously Reported Cutoff Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-PF</td>
<td>$&gt;2.9 \text{ g/dL}$</td>
<td>$&gt;3 \text{ g/dL}^{2}$</td>
</tr>
<tr>
<td>P-R</td>
<td>$&gt;0.5$</td>
<td>$&gt;0.5^{3}$</td>
</tr>
<tr>
<td>LDH-PF</td>
<td>$&gt;0.45$ of upper limits of normal</td>
<td>$&gt;200 \text{ IU/L}^{3,18}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$&gt;2/3$ of upper limits of normal$^{4}$</td>
</tr>
<tr>
<td>LDH-R</td>
<td>$&gt;0.6$</td>
<td>$&gt;0.6^{3}$</td>
</tr>
<tr>
<td>C-PF</td>
<td>$&gt;45 \text{ mg/dL}$</td>
<td>$&gt;45 \text{ mg/dL}^{18}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$&gt;54 \text{ mg/dL}^{25}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$&gt;55 \text{ mg/dL}^{26}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$&gt;60 \text{ mg/dL}^{19,22}$</td>
</tr>
<tr>
<td>C-R</td>
<td>$&gt;0.3$</td>
<td>$&gt;0.3^{16,19,22,25,26}$</td>
</tr>
<tr>
<td>A-G</td>
<td>$\leq1.2 \text{ g/dL}$</td>
<td>$\leq1.2 \text{ g/dL}^{16,23}$</td>
</tr>
<tr>
<td>BILI-R</td>
<td>$&gt;0.6$</td>
<td>$&gt;0.6^{16,20}$</td>
</tr>
</tbody>
</table>

**BAYESIAN ANALYSIS TO THE RESCUE?**

**Pleural fluid results**
- Pleural fluid to serum protein ratio = 0.45
- Pleural fluid LDH (fraction of laboratory normal) = 0.65
- Pleural fluid to serum LDH ratio = 0.75

**Light’s criteria**
- Pleural fluid to serum protein ratio > 0.5, or
- Pleural fluid LDH (fraction of laboratory normal) > 0.67, or
- Pleural fluid to serum LDH ratio > 0.6

**Calculation of posttest probability**
- Pretest probability of an exudate = 20%
- Pretest odds = pretest probability/(1.00 - pretest probability) = 0.20/(1.00 - 0.20) = 0.25
- Pleural fluid protein ratio LR = 0.49 (Table 2)
- Posttest odds₁ = pretest odds × LR = 0.25 × 0.49 = 0.12
- Pleural fluid LDH = 2.12 (Table 3)
- Posttest odds₂ = 0.12 × 2.12 = 0.25
- LDH-R LR = 1.34 (Table 3)
- Posttest odds₃ = 0.25 × 1.34 = 0.34
- Posttest probability of an exudate = posttest probability/(1.00 + posttest probability) = 0.34/(1.00 + 0.34) = 0.25 = 25%
TOOLS TO ASSESS MISCLASSIFIED TRANSUDATES

• Use of clinical judgment and response to therapy

• Use of tests to exclude an exudate
  • Serum-pleural protein gradient > 3.1g/dl
  • Serum-pleural albumin gradient > 1.2 g/dl
  • Pleural/serum albumin ratio < 0.6
  • Combined pleural LDH < 2/3 ULN, albumin gradient, and protein gradient

Bielsa S et al. Respirology 2012

Kummerfeldt CE et al. Chest 2014
# PROTEIN VS ALBUMIN GRADIENT?

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of transudates/ HF/HH</th>
<th>Misclassified transudates by Light’s criteria, No. (%)</th>
<th>Misclassified transudates with protein gradient &gt;3.1 g/dl, No. (%)</th>
<th>Misclassified transudates with albumin gradient &gt;1.2 g/dl, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth et al. [13]</td>
<td>18/15/1</td>
<td>5 (28)</td>
<td>ND</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Akkurt et al. [14]</td>
<td>27/24/0</td>
<td>5 (19)</td>
<td>ND</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Burgess et al. [15]</td>
<td>123/84/ND</td>
<td>19/112 (17)</td>
<td>ND</td>
<td>13 (68)</td>
</tr>
<tr>
<td>Gonlugur et al. [16]</td>
<td>71/62/0</td>
<td>28 (39)</td>
<td>20/26 (78)</td>
<td>25/26 (96)</td>
</tr>
<tr>
<td>Han et al. [17]</td>
<td>98/82/16</td>
<td>32 (33)</td>
<td>18/28 (64)</td>
<td>ND</td>
</tr>
<tr>
<td>Bayram et al. [18]</td>
<td>54/51/2</td>
<td>19 (37)</td>
<td>13 (68)</td>
<td>14 (74)</td>
</tr>
<tr>
<td>Bielsa et al. [7**]</td>
<td>466/364/102</td>
<td>125/466 (27)</td>
<td>70/123 (57)</td>
<td>37/49 (76)</td>
</tr>
<tr>
<td>Total</td>
<td>857/682/121</td>
<td>233/846 (27.5)</td>
<td>121/196 (62)</td>
<td>99/123 (80.5)</td>
</tr>
</tbody>
</table>

TOOLS TO ASSESS MISCLASSIFIED TRANSUDATES

- Use of tests to confirm an exudate
  - Pleural LDH > 2/3 ULN (or 200)
  - Pleural cholesterol > 1.16-1.42 mmol/L
  - Pleural / serum cholesterol ratio > 0.3
    Shen Y et al. BMC Pulm Med meta-analysis 2014

- Use of pleural or blood NT-pro-BNP > 1500 pg/ml
  Han ZJ et al. PLoS One Meta-analysis 2015
BOTTOM LINE

- In the case of a suspected transudative effusion classified as an exudate by Light’s criteria
  - Clinical judgment and response to therapy is the gold standard
  - In cases where doubt remains, the sequential use of additional fluid analyses can help
    - Albumin gradient
    - LDH < 2/3 ULN, albumin gradient, protein gradient combo
    - LDH > 2/3 ULN or 200 UI
    - Pleural fluid cholesterol and ratio to serum
    - Pleural or blood NT-pro-BNP (for CHF effusions)
MR D 86 YEARS-OLD MALE WITH A STERILE LYMPHOCYCTIC PLEURAL EXUDATE

- Pleural fluid analyses:
  - 60% lymphocytes
  - Unrevealing microbiology
  - LDH 230/180
  - Protein 35/66
  - Glucose 6.2
  - pH 7.34

Benign cytology
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help

or

Open poll in your web browser
PLEURAL FLUID ANALYSIS IN MALIGNANT EFFUSIONS

- **Classic picture**
  - Sterile exudate
  - Lymphocytic predominance (＞50% of WBC)
  - Can be bloody, but not a true hemothorax
  - pH, glucose can be low

- **Atypical features**
  - Transudate
  - Eosinophilic effusion (≥10% of WBC)
  - Increased salivary amylase
  - Chylothorax
PLEURAL FLUID CYTOLOGY & MALIGNANCY

- Overall sensitivity of approximately 60-72%
  - Varies from 40-87%  

  Light RW. Pleural Diseases 2013
  ACCP Lung Cancer Diagnosis Guidelines 2013

- Sensitivity is generally lower for mesothelioma

- Immunohistochemistry can specify the primary site in most cases
  - Ancillary molecular / genetic studies are reliable

- Amount of fluid sent has little impact on sensitivity
  - But the use of cell block increases sensitivity

Swidereck J et al. Chest 2010
Abouzheib W et al. Chest 2009
PLEURAL CYTOLOGY: VALUE OF REPEAT TAP

• The true sensitivity of a 2nd and 3rd thoracentesis are not known

• Of malignant effusions diagnosed through cytology:
  • 65-91% of diagnoses are made on the initial aspiration
  • 2nd tap provides a diagnosis in 2-27% of cases
  • 3rd tap provides a diagnosis in 0-6% of cases

Porcel JM et al. Arch Bronconeumol 2014
Garcia LW et al. Mod Pathol 1994
Johnston WW et al. Cancer 1985
Light RW Arch Int Med 1973
TAKE HOME MESSAGE

• When a malignant effusion is suspected and the initial thoracentesis is non-diagnostic, a 2\textsuperscript{nd} tap may help establish the diagnosis.

• However, a 3\textsuperscript{rd} pleural tap is unlikely to provide a diagnosis and should not be performed in most patients.
MR D 86 YEARS-OLD MALE WITH A STERILE LYMPHOCYTIC PLEURAL EXUDATE

- **PMHx:** HTN, A fib, BPH, heart murmur

- **Rx:** ASA, furosemide, ramipril, tamsulosin

- Born in Romania

- Non-smoker

- Retired engineer
MR D 86 YEARS-OLD MALE WITH A STERILE LYMPHOCYTIC PLEURAL EXUDATE
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help
or
Open poll in your web browser
THE ROLE OF CHEST CT IN UNDIAGNOSED EFFUSIONS

- Several CT features are suggestive of malignancy
  - Pleural nodules and masses
  - Mediastinal pleural thickening
  - Parietal pleural thickening > 1 cm
  - Circumferential pleural thickening
  - Suspicious lung lesions, evidence of extra-thoracic metastases
THE REAL-LIFE VALUE OF CHEST CT

Use of the CT report (suggestive of malignancy vs not) in patients with an undiagnosed effusion referred for pleural biopsy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Total no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained effusion</td>
<td>69% (62% to 76%)</td>
<td>78% (72% to 85%)</td>
<td>80% (74% to 87%)</td>
<td>66% (59% to 74%)</td>
<td>326</td>
</tr>
<tr>
<td>Effusion in known/previous malignancy</td>
<td>64% (47% to 82%)</td>
<td>75% (54% to 96%)</td>
<td>82% (66% to 98%)</td>
<td>55% (34% to 75%)</td>
<td>44</td>
</tr>
<tr>
<td>Overall</td>
<td>68% (62% to 75%)</td>
<td>78% (72% to 84%)</td>
<td>80% (75% to 86%)</td>
<td>65% (58% to 72%)</td>
<td>370</td>
</tr>
</tbody>
</table>

A CT showing no signs of malignancy does not preclude further investigations

Halifax RJ et al. Thorax 2015
ANOTHER SCORE TO THE RESCUE?

<table>
<thead>
<tr>
<th>Parameters</th>
<th>OR (95% CI)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any pleural lesion(\geq 1) cm</td>
<td>250 (24-2,650)</td>
<td>5</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>30.7 (6-156)</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>15.3 (4-65)</td>
<td>3</td>
</tr>
<tr>
<td>Lung mass or lung nodule/(\leq 1) cm</td>
<td>12.2 (5-29)</td>
<td>3</td>
</tr>
<tr>
<td>Absence of pleural loculations</td>
<td>4.3 (2-9)</td>
<td>2</td>
</tr>
<tr>
<td>No pericardial effusion</td>
<td>23.5 (1-626)</td>
<td>2</td>
</tr>
<tr>
<td>Nonenlarged cardiac silhouette</td>
<td>9.3 (2-48)</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>LR Positive (95% CI)</th>
<th>LR Negative (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\geq 5) or 6</td>
<td>93 (87-96)</td>
<td>68 (61-73)</td>
<td>2.9 (2.4-3.5)</td>
<td>0.10 (0.05-0.20)</td>
</tr>
<tr>
<td>(\geq 7)</td>
<td>74 (65-81)</td>
<td>92 (88-95)</td>
<td>9.4 (5.9-14.8)</td>
<td>0.28 (0.21-0.39)</td>
</tr>
<tr>
<td>(\geq 8) or 9</td>
<td>59 (50-68)</td>
<td>97 (94-99)</td>
<td>22.5 (10.1-50.2)</td>
<td>0.42 (0.34-0.52)</td>
</tr>
<tr>
<td>(\geq 10)</td>
<td>29 (21-38)</td>
<td>100 (98-100)</td>
<td>65.4 (9.1-472.3)</td>
<td>0.72 (0.64-0.80)</td>
</tr>
</tbody>
</table>

Porcel JM et al. Chest 2015
THE ISSUE OF PULMONARY EMBOLISM

- A pleural effusion is present in 20-48% of acute PE
  - >90% of effusions are small
  - Most are unilateral
  - Most are ipsilateral to the PE
  - But large, bilateral, or contralateral effusions also reported

Yap E et al. Respirology 2008
Porcel JM et al. Respirology 2007

- PE is often cited as a common cause of pleural effusion, with little supporting evidence

Light RW. Pleural Diseases Textbok 6th ed. 2013
THE ISSUE OF PULMONARY EMBOLISM

• In a prospective study using CT-angiogram and pleural-phase CT in all consecutive patients referred for evaluation of a new unilateral effusion (n=141)
  • 9 patients had a confirmed PE (6.4%)

• Of the patients with a PE, 8/9 were diagnosed with cancer

• The PE was not thought to be the cause of the effusion in any of the 9 patients, but may have contributed in 2 cases

Hooper C et al. Respiration 2014
THE ROLE OF PET SCANNING

- 3 meta-analyses studied the value of PET scan for the diagnosis of pleural malignancy with varying results

- The literature is afflicted by several limitations
  - Most studies included patients with pleural anomalies
  - All studies were small and usually from a single center
  - Few studies included enough benign inflammatory conditions
  - No outcome-based data available

- PET, PET/CT, qualitative and semi-quantitative methods are different tests with distinct diagnostic characteristics

- The diagnostic, therapeutic, and prognostic implications are too great to forego the need for tissue confirmation
PET SCANNING IS NOT GOOD ENOUGH

**TABLE 3** Summary Measures of Diagnostic Accuracy for FDG-PET Imaging in the Identification of Malignant Pleural Effusions

<table>
<thead>
<tr>
<th>Measure</th>
<th>Qualitative PET Imaging Readings</th>
<th>Semiquantitative PET Imaging Readings</th>
<th>Qualitative Readings Using PET Imaging Systems</th>
<th>Qualitative Readings Using Integrated PET-CT Imaging Systems</th>
<th>Semiquantitative Readings Using Integrated PET-CT Imaging Systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies, No.</td>
<td>11</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Sensitivity (95% CI), %</td>
<td>91 (86-94)</td>
<td>82 (69-90)</td>
<td>96 (90-98)</td>
<td>89 (81-94)</td>
<td>81 (66-91)</td>
</tr>
<tr>
<td>Specificity (95% CI), %</td>
<td>67 (56-77)</td>
<td>74 (62-84)</td>
<td>75 (59-87)</td>
<td>61 (44-75)</td>
<td>74 (58-85)</td>
</tr>
<tr>
<td>Positive LR (95% CI)</td>
<td>2.83 (2.04-3.98)</td>
<td>3.24 (2.24-4.70)</td>
<td>4.09 (2.34-7.1)</td>
<td>2.32 (1.61-3.45)</td>
<td>3.22 (2-5)</td>
</tr>
<tr>
<td>Negative LR (95% CI)</td>
<td>0.14 (0.08-0.22)</td>
<td>0.25 (0.14-0.39)</td>
<td>0.06 (0.03-0.13)</td>
<td>0.19 (0.11-0.31)</td>
<td>0.26 (0.14-0.43)</td>
</tr>
<tr>
<td>DOR (95% CI)</td>
<td>22 (10.2-41.7)</td>
<td>13.8 (7.3-23.9)</td>
<td>76.7 (22.1-195)</td>
<td>13 (6-24.8)</td>
<td>13.3 (6.32-24.8)</td>
</tr>
<tr>
<td>AUC</td>
<td>0.893</td>
<td>0.840</td>
<td>0.950</td>
<td>0.859</td>
<td>0.838</td>
</tr>
</tbody>
</table>

Porcel JM et al. Chest meta-analysis 2015
BOTTOM LINE

• Although certain CT features can be very suggestive of malignancy, a CT without such features does not exclude a malignant effusion or pleural tuberculosis

• Even if malignant features are seen on a CT, a tissue diagnosis is still required for confirmation and treatment planning (in most cases)

• A PET/CT scan should not be routinely included in the investigation of an undiagnosed effusion
WHEN AND HOW TO SCAN?

- Performance of imagery before or after the initial pleural drainage procedure does not alter the information obtained or the management
  
  Corcoran JP et al. Respirology 2016

- Unless contra-indicated, a contrast chest CT with upper abdominal cuts should be done
  
  • A delayed phase protocol is ideal to better enhance the pleura (45-60s delay)
  • Whether to also perform a CT pulmonary angiogram is controversial

Hooper C et al. Respiration 2014
BIOMARKERS IN UNDIAGNOSED PLEURAL EFFUSION

• For the diagnosis of carcinoma and mesothelioma, a variety of biomarkers have been proposed
  • Pleural CEA, survivin, serum or pleural fibulin-3, soluble mesothelin...

• For pleural tuberculosis, pleural adenosine deaminase (ADA) is a sensitive and specific marker
  • Sn 92%, Sp 90% with a cut-off of 40 U/L
  • Also elevated in parapneumonic effusions and lymphoma
  • Excellent negative predictive value in low incidence settings

Liang QL et al. Respir Med 2008
MR D 86 YEARS-OLD MALE WITH A STERILE LYMPHOCYTIC PLEURAL EXUDATE

- **PMHx**: HTN, A fib, BPH, heart murmur
- **Rx**: ASA, furosemide, ramipril, tamsulosin
- No malignant features on CT
- Benign cytology x 2
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help
or
Open poll in your web browser
PERCUTANEOUS PLEURAL BIOPSY

• Conventional Abrams pleural biopsy has a Sn of approx 57% for malignancy, and 60-80% for TB
  • The added yield to cytology varies from 7-27%
  • Its diagnostic yield is inferior to thoracoscopic biopsy

Roberts ME et al. BTS Guidelines 2010

• The use of ultrasound or CT guidance greatly increases the diagnostic value of pleural biopsy

Sconfienza LM et al. Radiology 2012
Maskell N et al. Lancet 2003
Metintas M et al. Chest 2010

• Several different image-guided techniques are available
  • US or CT-guided, Abrams or cutting needle biopsy

• The diagnostic yield & sensitivity is however limited in the absence of pleural nodules or thickening > 1cm

Metintas M et al. Respiration 2016
MEDICAL THORACOSCOPY

• Outpatient procedure done under conscious sedation by respirologists using a single port of entry

• Considered the test of choice for undiagnosed exudative effusions
  
  • Pooled Sn for malignancy of 93% (>90% for mesothelioma)
  • Pooled Sn for tuberculosis of 93%
  • Mortality of 0.34%
  • Major complications in 1.8% (empyema, pneumonia, hemorrhage)

• No direct comparison between VATS and medical thoracoscopy however

Systematic review of 22 series. Roberts ME et al. BTS Guidelines 2010
MEDICAL THORACOSCOPY

Rigid thoracoscope

Semi-flexible thoracoscope

Karl Storz Catalogue

Ernst A et al. CHEST 2002
MALIGNANT EFFUSIONS

Loddenkemper R et al. Medical Thoracoscopy/Pleuroscopy: Manual and atlas. Thieme 2011
TUBERCULOUS EFFUSIONS

Loddenkemper R et al. Medical Thoracoscopy/Pleuroscopy: Manual and atlas. Thieme 2011
DIAGNOSTIC MEDICAL
THORACOSCOPY: LIMITATIONS

• Thoracoscopist’s skills and experience
  • How to biopsy? Where and what to biopsy?
  • Ability to manoeuvre through adhesions

• Incomplete pleural inspection due to adhesions

• Patchy pleural involvement with a low burden of disease

• Many causes of pleural exudates produce only a non-specific pleuritis on histology
THORACOSCOPIC BIOPSY: ADVANTAGES

• Allows sampling of multiple sites through direct visualization

• Preserved diagnostic yield in the absence of pleural anomaly on imagery

• Allows the performance of therapeutic measures in the case of a symptomatic malignant effusion
  • Talc pleurodesis
  • Indwelling pleural catheter insertion
  • Indwelling pleural catheter insertion + talc
The diagnostic test of choice after one (or 2) non-diagnostic pleural cytology depends on multiple factors:

- Appearance of pleura on imaging
- Local expertise and availability of tests
- Likelihood of alternative causes for the effusion
- Patient comorbidities
- Need for therapeutic procedure

Where available, medical thoracoscopy is a simple, safe and highly accurate diagnostic tool.
MR D 86 YEARS-OLD MALE WITH A STERILE LYMPHOCYTIC PLEURAL EXUDATE

- No malignant features on CT
- Benign cytology x 2
- Medical thoracoscopy showed multiple parietal pleural nodules
  - Biopsy: adenocarcinoma of lung origin
WHAT TO DO WITH A BENIGN PLEURAL BIOPSY?
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help
or
Open poll in your web browser
NON-SPECIFIC PLEURITIS

• The category of non-specific pleuritis is common and encompasses a wide variety of histological descriptions
  • Fibrinous or follicular pleuritis / non-specific pleuritis
  • Reactive pleuritis / organizing pleuritis
  • Benign pleuritis / pleuritis with mesothelial cell hyperplasia

• Can be encountered in numerous conditions
  • Drug-induced, radiotherapy-related effusion
  • Inflammatory conditions
  • Benign asbestos effusion
  • Idiopathic pleuritis

• Close follow up is necessary; duration unclear, but at least 2yrs
  • ~8% of patients will develop a malignancy, most often a mesothelioma
NON-SPECIFIC PLEURITIS REQUIRES FOLLOW UP FOR AT LEAST 2 YRS

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Pleural biopsy procedure</th>
<th>Number of patients undergoing biopsy</th>
<th>Histological aetiological diagnosis post biopsy</th>
<th>NSP on biopsy</th>
<th>NSP follow-up period (months)</th>
<th>Likely cause established during follow-up in NSP group</th>
<th>Final diagnosis of malignancy in NSP group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryan et al. [14]</td>
<td>1981</td>
<td>Thoracotomy</td>
<td>NS</td>
<td>NS</td>
<td>51 patients</td>
<td>18-180</td>
<td>35%</td>
<td>25%</td>
</tr>
<tr>
<td>Hansen et al. [10]</td>
<td>1998</td>
<td>Thoracoscopy</td>
<td>147</td>
<td>69%</td>
<td>31%</td>
<td>≥24</td>
<td>27%</td>
<td>NS</td>
</tr>
<tr>
<td>Blanc et al. [8]</td>
<td>2002</td>
<td>Thoracoscopy</td>
<td>154</td>
<td>56%</td>
<td>38%</td>
<td>≥12</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Janssen et al. [15]</td>
<td>2004</td>
<td>Thoracoscopy</td>
<td>709</td>
<td>NS</td>
<td>55%</td>
<td>≥24</td>
<td>55%</td>
<td>8%</td>
</tr>
<tr>
<td>Venekamp et al. [16]</td>
<td>2005</td>
<td>Thoracoscopy</td>
<td>NS</td>
<td>NS</td>
<td>60 patients</td>
<td>34.8 (±27.1)</td>
<td>75%</td>
<td>8%</td>
</tr>
<tr>
<td>Davies et al. [12**]</td>
<td>2010</td>
<td>Thoracoscopy</td>
<td>142</td>
<td>69%</td>
<td>31%</td>
<td>21.3 (±12.0)</td>
<td>38%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Wrightson JM, Davies HE. Curr Opin Pulm Med 2011
1. Recognize that a high percentage of pleural effusion diagnoses are unclear after initial assessment

2. Describe the approach, diagnosis and investigation for a pleural effusion of unknown cause

3. Define the role of imagery and/or pleural biopsy in the setting of pleural effusion of unknown cause
TAKE HOME MESSAGE: THE BASICS

• Because the differential diagnosis is wide and the basic fluid analyses non-specific, a systematic approach to pleural effusions is necessary

  • It should include a thorough occupational history with a search for asbestos exposure

• In the absence of long-standing RA, a lymphocytic effusion with a low pH and / or glucose is caused by malignancy or TB until proven otherwise
TAKE HOME MESSAGE: TRANSUDATE MISSCLASSIFICATION

- In the case of a suspected transudative effusion classified as an exudate by Light’s criteria
  - Clinical judgment and response to therapy is the gold standard
  - In cases where doubt remains, the sequential use of additional fluid analyses can help
    - Albumin gradient
    - LDH < 2/3 ULN, albumin gradient, protein gradient combo
    - LDH > 2/3 ULN or 200 UI
    - Pleural fluid cholesterol and ratio to serum
    - Pleural or blood NT-pro-BNP (for CHF effusions)
TAKE HOME MESSAGE: VALUE OF PLEURAL FLUID CYTOLOGY

• The sensitivity of pleural fluid cytology is ~ 60%, and lower for mesothelioma

• When a malignant effusion is suspected and the initial thoracentesis is non-diagnostic, a 2nd tap may help establish the diagnosis

• However, a 3rd pleural tap is unlikely to provide a diagnosis and should not be performed in most patients
TAKE HOME MESSAGE: RADIOLOGY

- Although certain CT features can be very suggestive of malignancy, a CT without such features does not exclude a malignant effusion or pleural tuberculosis.

- Even if malignant features are seen on a CT, a tissue diagnosis is still required for confirmation and treatment planning (in most cases).

- A PET/CT scan should not be routinely included in the investigation of an undiagnosed effusion.
TAKE HOME MESSAGE: PLEURAL BIOPSY

• The diagnostic test of choice after one (or 2) non-diagnostic pleural cytology depends on multiple factors:
  
  • Appearance of pleura on imaging
  • Local expertise and availability of tests
  • Likelihood of alternative causes for the effusion
  • Patient comorbidities
  • Need for therapeutic procedure

• Where available, medical thoracoscopy is a simple, safe and highly accurate diagnostic tool
« THE GOOD PHYSICIAN TREATS THE DISEASE; THE GREAT PHYSICIAN TREATS THE PATIENT WHO HAS THE DISEASE »

SIR WILLIAM OSLER