Pleural Effusions: a case-based review

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Disclosure

• None
Outline

• Normal pleural anatomy and function
• Mechanisms of pleural fluid accumulation
  – Transudates vs. Exudates
• Evaluating pleural effusions
  – Imaging
  – Thoracentesis
  – Pleural fluid analysis
• Diagnosis and management of common exudative effusions
• Evaluating the exudative effusion of unknown etiology
Normal Pleural Anatomy

- Basal pleural fluid volume: \( \sim 2.0 \text{ ml/hr} \)
  - Daily production: \( \sim 25 \text{ ml/day} \)

- Drainage capacity: \( \sim 15 \text{ ml/hour} \)
  - Daily absorption: \( \sim 350 \text{ ml/day} \)
First Case

- 67 year old man with dyspnea and cough x 2 months
- Exam: poor chest excursion on the R with absent BS
- US of the R chest: small pleural effusion
- Pleural Fluid Analysis:
  - PF protein 3.9 (serum 7.9)
  - LDH 200 (serum 250)
  - Glucose 98
  - pH 7.48
  - GS, Cultures AFB smear NEG
  - Cytology NEG

Lung markings are present here (over-exposed)!
First Case

The next step in managing this patient is:
A. Perform a large volume thoracentesis
B. Place an indwelling pleural catheter
C. Thoracoscopy with pleural biopsy
D. Perform a bronchoscopy
E. B and D
Pleural Effusions from “trapped lung”
Pleural Fluid Origins: *Trapped Lung*

- **Parietal**
  - NL $P_{\text{hydrostatic}}$
  - Blood Vessel
  - Pleural Space
  - Serous
  - Fluid
  - $P_{\text{pleura}} = -25 \text{ cmH}_2\text{O}$

- **Visceral**
  - NL $P_{\text{hydrostatic}}$

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**NL**

**Blood Vessel**

**Pleural Space**

**Serous**

**Fluid**

**$P_{\text{pleura}} = -25 \text{ cmH}_2\text{O}$**
Entrapped v. Trapped Lung

Manometry

Normal

Entrapped Lung

Trapped Lung

PRESSURE (cm H2O)

VOLUME (ml)
Causes of TRANSUDATIVE Pleural Effusions

• Congestive Heart Failure (40%)
• Cirrhosis
• Nephrotic Syndrome
• Trapped Lung (also can be exudative)
• Pulmonary Embolism (also can be exudative)
• Myxedema
• Urinothorax
• CSF leak
Causes of EXUDATIVE Pleural Effusions

- Parapneumonic / empyema (25%)
- Malignancy (12%)
- PE (10%)
- Tuberculosis
- Pancreatitis
- RA, SLE

- Uremia
- Post-cardiac injury / surgery
- Asbestos
- Chylothorax
- Intra-abdominal Abscess
- Meig’s Syndrome
Diagnostic Evaluation of Pleural Effusions

• Identifying the etiology of a pleural effusion requires:
  • CLINICAL information
    – To suggest an underlying diagnosis
  • Radiographic findings
    – Infiltrate, mass, lymphadenopathy
  • Pleural fluid analysis
    – Transudate v. Exudate ->
      • Cell count and differential, cytology, culture, etc....
Pleural Effusions: When to Tap

Pleural effusion

Substantial fluid? (≥10 mm thick on lateral decubitus CXR)

No
Observation

Yes
CHF?

No
Thoracentesis

Yes
Asymmetry, chest pain, fever?

Yes -> Thoracentesis

No
Diuresis, Observation

Effusion > 3 days -> Thoracentesis
The Value of the Lateral Film

Up to 500 ml can be “hidden” on an AP film

Effusion!
Large Volume Thoracentesis: OK to remove > 1 liter??

185 pts with 1L -> 3.5L removed

- 1 pt (0.5%) had symptomatic re-expansion pulmonary edema (RPE) [1.4L removed]
- 4 pts (2.2%) had radiographic RPE only
- RPE did not correlate with pleural fluid volume, end-expiratory pleural pressure, or symptoms during the procedure
- No clear guidelines, but RPE is rare and strict adherence to limiting thoracenteses to 1L is not supported by data

Transudate or Exudate?:
Light’s criteria

- Distinguish transudate from exudate

- One or more of the following defines an exudate:
  - Pleural fluid (PF) protein : Serum protein > 0.5
  - PF LDH : Serum LDH > 0.6
  - PF LDH > 2/3 upper limit normal serum LDH
Transudate or Exudate?

• If you truly suspect a transudate (e.g. a “diuresed” CHF-related effusion), check...

  – Serum - PF protein > 3.1 gm/dL
  – Serum– PF albumin gradient > 1.2 gm/dL

  – Then = TRANSUDATE

### Transudate or Exudate?

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity*</th>
<th>Specificity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF: serum protein &gt; 0.5</td>
<td>98%</td>
<td>83%</td>
</tr>
<tr>
<td>PF: serum LDH &gt; 0.6</td>
<td>86%</td>
<td>84%</td>
</tr>
<tr>
<td>PF LDH &gt; 2/3 nl serum</td>
<td>90%</td>
<td>82%</td>
</tr>
<tr>
<td>Serum-PF alb &lt; 1.2</td>
<td>87%</td>
<td>92%</td>
</tr>
</tbody>
</table>
37 year old woman with:

- 2 months of dry cough
- Dyspnea on exertion
- R anterior pleuritic chest pain
Pleural Fluid Analysis

Pleural Fluid:

LDH: 459

pH: 7.37

glucose: 72

WBC: 900  Diff: 27N 28M 40L 5 mesothelial cells

RBC: too numerous to count

Fluid hematocrit: 22%
# Grossly Bloody Pleural Fluid

<table>
<thead>
<tr>
<th>Fluid Hematocrit</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>Not significant</td>
</tr>
<tr>
<td>1-20% (hemorrhagic process)</td>
<td>Cancer &gt;&gt; PE &gt; Trauma &gt; empyema</td>
</tr>
<tr>
<td>20 – 50%</td>
<td>Hemorrhagic process v. Hemothorax</td>
</tr>
<tr>
<td>&gt;50% circulating HCT</td>
<td>Hemothorax</td>
</tr>
</tbody>
</table>
Spontaneous Bloody Effusions and Hemothorax

BLOODY Pleural effusion
- No Trauma
- No Procedures

Pleural Fluid HCT < 50% of peripheral blood HCT

Etiologies
- Lung Ca
- PE - pulmonary infarction
- Tuberculosis

Hemorrhagic Empyema
- Uremia
- Coagulopathy
- Mesothelioma

Pleural Fluid HCT > 50% of peripheral blood HCT (frank hemothorax)

BLOODY Pleural effusion
- No Trauma
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- No Trauma
- No Procedures

- Pleural Fluid HCT < 50% of peripheral blood HCT
- Pleural Fluid HCT > 50% (frank hemothorax)

**CT Angiogram or MRA**

**NON-vascular**
- Endometriosis
- Pleural Metastases
- Angiosarcomas
- Thymoma / Thymic cysts
- Chest wall
- Bony anomaly "Exostoses"
Spontaneous Bloody Effusions and Hemothorax

**BLOODY Pleural effusion**
- No Trauma
- No Procedures

- Pleural Fluid HCT < 50% of peripheral blood HCT
  - **Etiologies**
    - Lung Ca
    - PE - pulmonary infarction
    - Tuberculosis
    - Hemorrhagic Empyema
    - Uremia
    - Coagulopathy
    - Mesothelioma

- Pleural Fluid HCT > 50% of peripheral blood HCT (frank hemothorax)
  - CT Angiogram or MRA
  - Pleural Fluid HCT > 50% of peripheral blood HCT (frank hemothorax)

**Vascular Anomalies**
- AVM's
- Neurofibromatosis
- Aneurysms (intercostal, IMA)
- Endometriosis
- Pleural Metastases
- Angiosarcomas
- Thymoma / Thymic cysts

**NON-vascular**
- Chest wall
- Bony anomaly
- "Exostoses"
Back to the case...

- R VATS with pleural biopsy and wedge resection
  - hemothorax > 1 L
  - Endometrial tissue
  - Lung

- **Thoracic Endometriosis**
Another Case!

- 72 year old man with 2 days of
  - Intense R sided chest pain, dry cough, chills and dyspnea
- Exam
  - T 100.9, Decreased BS right base
- Labs
  - Serum WBC 15K (80 poly’s, 10% bands)
- Lateral Decubitus CXR revealed a flowing moderate-sized effusion
- Blood cultures were obtained and Antibiotics started
Quick Quiz

• Thoracentesis ->
• Pleural Fluid Analysis
  – Sero-sanguinous
  – PF protein 3 (serum 4)
  – PF LDH 800 (serum 300)
  – PF pH 7.18
  – Gram stain and cultures NEG

The most likely infection in this case is:

A. S. pneumoniae
B. S. milleri
C. H. influenza
D. S. aureus
E. A or C
Microbiology of COMMUNITY-Acquired Pleural Infections

- Strep Milleri 32%
- S. Pneumoniae 13%
- Staphylococci 11%
- Anaerobes 16%
- Other 18%
- H. Flu 3%
- Enterobacter 7%
Quick Quiz

• Thoracentesis ->
• Pleural Fluid Analysis
  – Sero-sanguinuous
  – PF protein 3 (serum 4)
  – PF LDH 800 (serum 300)
  – PF pH 7.18
  – Gram stain and cultures NEG

The next step in managing this effusion is:

A. Antibiotics and close observation, including daily CXRs
B. Thoracentesis to drain the pleural space
C. VATS decortication
D. Chest tube drainage +/- fibrinolytics to the pleural space
E. A or D
COMPLICATIONS of Parapneumonic Effusions:  

*why drain?*

- Chronic Pleural Infection
- Secondary Lung Abscess
- Bronchopleural Fistula
- Empyema Necessitans
  - Pleuro-cutaneous fistula

- Pleural Fibrosis
  - Lung entrapment →
  - Impaired lung function →
  - Surgical decortication
<table>
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<tr>
<th>Pleural Anatomy</th>
<th>Fluid Micro</th>
<th>Fluid pH</th>
<th>Risk of Poor outcome</th>
<th>Drain?</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 mm on Lat decub</td>
<td>N/A</td>
<td>N/A</td>
<td>LOW</td>
<td>No</td>
</tr>
<tr>
<td>CXR</td>
<td></td>
<td></td>
<td></td>
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<td>----------------</td>
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<td>---------</td>
</tr>
<tr>
<td>&lt;10 mm on Lat decub CXR</td>
<td>N/A</td>
<td>N/A</td>
<td>LOW</td>
<td>No</td>
</tr>
<tr>
<td>&lt; ½ hemithorax AND -&gt;</td>
<td>GS and Cx NEG AND -&gt;</td>
<td>pH &gt; 7.20</td>
<td>LOW</td>
<td>No, BUT need to follow</td>
</tr>
<tr>
<td>&gt; ½ hemithorax, loculated, thick pleura Or -&gt;</td>
<td>GS or Cx + Or -&gt;</td>
<td>pH &lt; 7.20</td>
<td>Moderate / High</td>
<td>YES</td>
</tr>
</tbody>
</table>
Treating Complex Parapneumonic Effusions / Empyema

• Definitive Pleural Drainage
  – Commonly via chest tube
  – Serial thoracenteses an alternative, but not well-studied

• Pleural Catheter + Fibrinolytics
  – Variably used and STILL requires individual assessment
  – Multicenter Intrapleural Sepsis Trial (MIST-1)
    • Pleural saline v. streptokinase
    • Streptokinase did NOT improve survival, need for surgical intervention, Chest CT appearance, or lung function
    • Additional fibrinolytic trial (s)....
Small Drainage Catheters + Fibrinolytic + DNA’se Treatment of Empyema

  – Pleural saline v. tPA v. DNAse v. tPA + DNAse x 3 days
  – tPA + DNAse group had decreased need for:
    • Surgical intervention (4% compared to 39% for placebo); and...
    • An improved CXR by day 7 and 30

**Important considerations with intra – pleural tPA**
~1.8% risk of pleural hemorrhage
Markedly simulates pleural fluid production (up to 6-fold)
Contraindicated in presence of broncho-pleural fistula
Treating Complex Parapneumonic Effusions / Empyema

• Surgical Decortication
  – Indicated if little clinical or radiographic improvement after 1 week of antibiotics and chest tube drainage +/- pleural lytics
  – Required in ~30% of cases
  – VATS adequate in 60% of these cases

• Appropriate Antibiotics
  – Duration uncertain: 2 weeks minimum, but as long as necessary for drains to be removed
  – Sometimes longer courses required for atypical pathogens (e.g. actinomyces) or in cases of prolonged pleural drainage
A Surprise Case...

- 53 year old man with hypertension, atrial fibrillation presents with: 2 months of acute on chronic exertional dyspnea

- 3+ pre-tibial lower extremity edema

- Orthopnea & paroxysmal nocturnal dyspnea, worse than baseline
Case CXR
### Thoracentesis

- **Removed:** 1200 cc
- **WBC:** 1650 \( (P_{14} L_{83} M_{2}) \)
- **pH:** 7.57
- **Glucose:** 262
- **Total Protein:** 3.9
- **Albumin:** 2.3
- **LDH:** 159
- **Gram stain/culture:** negative
- **Cytology:** negative
- **Cholesterol:** 77

**Triglycerides:** 1,276
Chylothorax?

Pleural Fluid Triglyceride level (mg/dl)

- >110 Chylothorax
- 50-110 Lipoprotein analysis
- <50 PSEUDO-Chylothorax (likely chronic exudate)

+ Chylomicrons -> CHYLOTHORAX

Traumatic

Chest trauma
Thoracic surgery

Non Traumatic

Lymphoma, solid tumors, chest XRT
Histoplasmosis, MTB, Sarcoid
Chylous ascites
LAM, yellow nail syndrome, Amyloid
L subclavian DVT
Filarialisis
Pseudo - Chylothorax

• **Pseudo - Chylothorax:** *Cholesterol*, phospholipid Complexes = from:
  Cell degradation, chronic exudate, empyema

  *Cholesterol* > 250 mg/dL
  + cholesterol crystals (rhomboid)
  $\text{TG}_{\text{fluid}}$ LOW

• **Chylothorax:**
  $\text{TG}_{\text{fluid}}$ > 110mg/dL
  $\text{TG}_{\text{fluid}}$ > $\text{TG}_{\text{serum}}$
  *Cholesterol* $\text{fluid}$ < 200 mg/dL
  + chylomicrons
Chyle Loss Increases Mortality

Fat
Vitamins A, D, E, K
Proteins
Immunoglobulins
Lymphocytes

Malnutrition
Immunosuppression

17-35% mortality (limited data)
4.5-fold ↑ risk of death in surgical patients

Fat
Vitamins A, D, E, K
Proteins
Immunoglobulins
Lymphocytes

Malnutrition
Immunosuppression

17-35% mortality (limited data)
4.5-fold ↑ risk of death in surgical patients
Management

↓ Chyle Flow
- No short- or long-chain TG intake
- Octreotide or Somatostatin

Maintain Nutrition
- Medium-chain TGs → enter portal circulation directly
- Total parental nutrition (TPN)

Remove Chyle
- Thoracentesis
- Tube Thoracostomy
- Pleuroperitoneal Shunt
- Pleurovenous Shunt

Close Chyle Leak
- Pleurodesis
- Duct Embolization
- Surgical Duct Ligation
Exudative Effusion of Unclear Etiology

- 46 year old man with a h/o myelodysplastic syndrome, s/p an unrelated allo-stem cell transplant: complicated by cutaneous and GI graft-versus-host disease

- NOW with dyspnea and progressive right-sided pleuritic chest pain x 2-3 weeks

- No fevers/chills, known sick contacts, or recent travel

- Medications: prednisone 20 mg daily, tacrolimus, atovaquone, valganciclovir
Chest X ray
Thoracentesis

• Labs:
  – Serum: LDH 229, Total Protein 6.5, Albumin 3.7
  – Fluid: LDH 226, Total Protein 4.1, Albumin 2.7
  – Fluid: pH 7.6, Glucose 208, Amylase 12
  – Fluid: ADA 3.1 (usually > 40 U/L in tuberculous pleural effusions)

• Cultures: AFB, Fungal, Aerobic/Anaerobic, Actinomyces, Nocardia, PCP all negative

• Cytology + flow cytometry negative for malignancy
Exudative Effusion of Unclear Etiology

• Up to 20% of exudative pleural effusions have no clear etiology, even after:
  – Pleural fluid analysis from thoracentesis and
  – Thoracoscopy and pleural biopsy

• Most undiagnosed exudates are from:
  – Malignancy (including mesothelioma)
  – Chronic empyema (including atypical organisms)
  – Tuberculosis
  – Rheumatoid Arthritis / inflammatory
  – Pulmonary Embolus
  – “Diuresed” CHF
Exudative Pleural Effusion

"Borderline" Exudate

- Serum:PF Albumin > 1.2 g/dL
- Pleural Fluid NT-proBNP > 2000 pg/mL
- Consider CHF, nephrosis, cirrhosis

All Other Exudates

- NEGATIVE
  - History
  - Microbiology
  - Cytology

- Consider PE (DDIMER, PE-CT)
  - Consider TB
  - ADA > 40 U/L or
  - IFN-gamma > 140 pg/mL

- NEGATIVE

- Thoracoscopy and Pleural Biopsy
Pleural Fluid Biomarkers: new diagnostic tools for idiopathic exudates

Back to the case... evaluation for Infection

- Blood cultures negative
- 1,3 Beta D-glucan <31
- Galactomannan 0.15 (negative)
- S pneumo and Legionella Urine Ag negative
- Histoplasma and Blastomyces Urine Ag negative
- Cryptococcal Ag negative
- CMV PCR (blood) negative
- PCP (sputum) negative
Bronchoscopy, Pleuroscopy and Pleural Biopsy

Methenamine Silver Stain (MSS) 100x

Modified AFB Stain 100x
Quick FINAL Case!

• 55 yo man with subacute dyspnea
  – History: EtOH
  – Exam: Decreased BS R chest,
    + Ascites
  – Pleural fluid analysis:
    • PF protein 1.0 (serum 3.0)
    • PF LDH 100 (serum 300)

• What is the etiology of the patient’s R-sided pleural effusion?
Quick FINAL Case: Answer

• Hepatic Hydrothorax
  – Occurs in ~7% of pts with ascites
  – Usually large R effusion (80% on R)
  – Forms due to rifts in the diaphragm
  – Can accumulate rapidly
  – 20% of HH can form without ascites
  – Tap pleural + peritoneal fluid (to r/o infection
    – “SBP” - and alleviate symptoms)
  – Treat underlying ascites and cirrhosis -> often difficult...
  – TIPS can be affective for refractory HH
Hepatic Hydrothorax: follow-up

- Spironolactone, furosemide, IV Albumin, and octreotide minimally effective –

- TIPS performed and discharged on diuretic regimen

- CXR 3 months later!
Further Reading


2. Light, RW. The Light Criteria The Beginning and Why they are Useful 40 Years Later. *Clin Chest Med* 2013; 34: 21-26


5. Porcel Jose M. Pearls and myths in pleural fluid analysis. *Respirology* 2011; **16**: 44