Brigham and Women's Hospital
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Pleural Effusions: a case-based review

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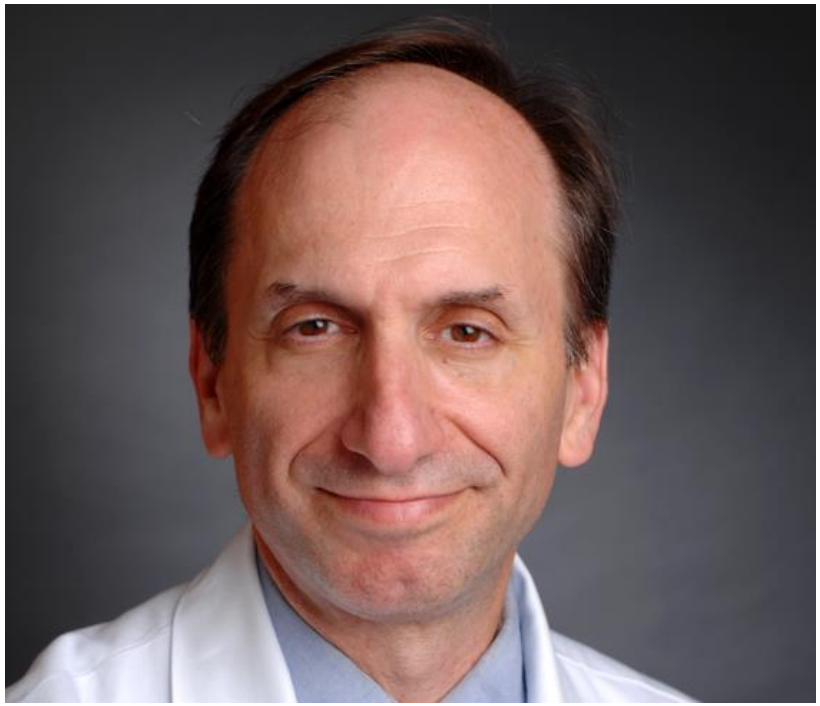
CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL



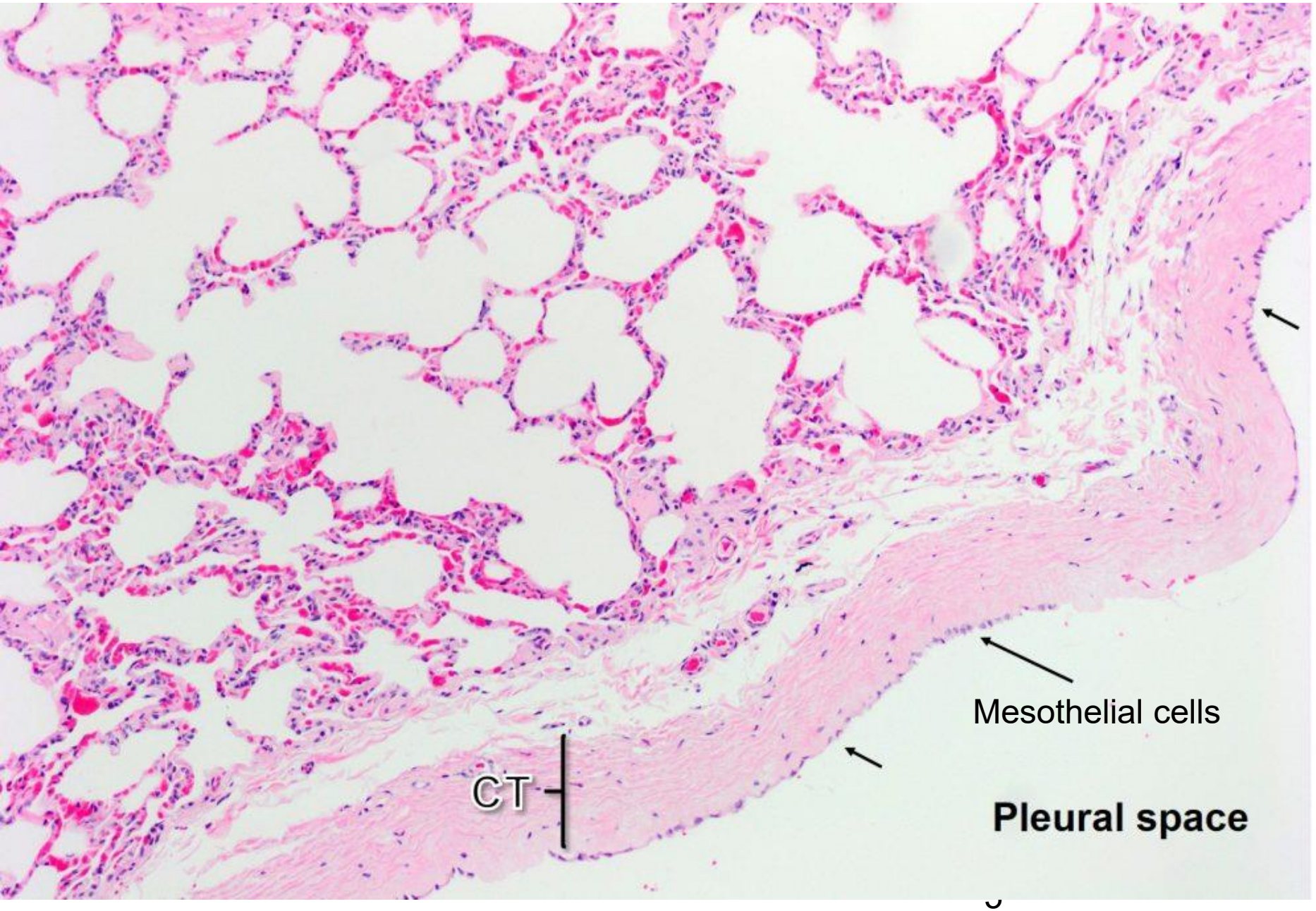
- UMDNJ-New Jersey Medical School
- Medicine Residency at Boston City Hospital
- Pulmonary/Critical Care fellowship at University of Pennsylvania
- Assistant Professor of Medicine at HMS
  - Clinical and research interest in sleep and delirium in the critically ill.

Disclosure

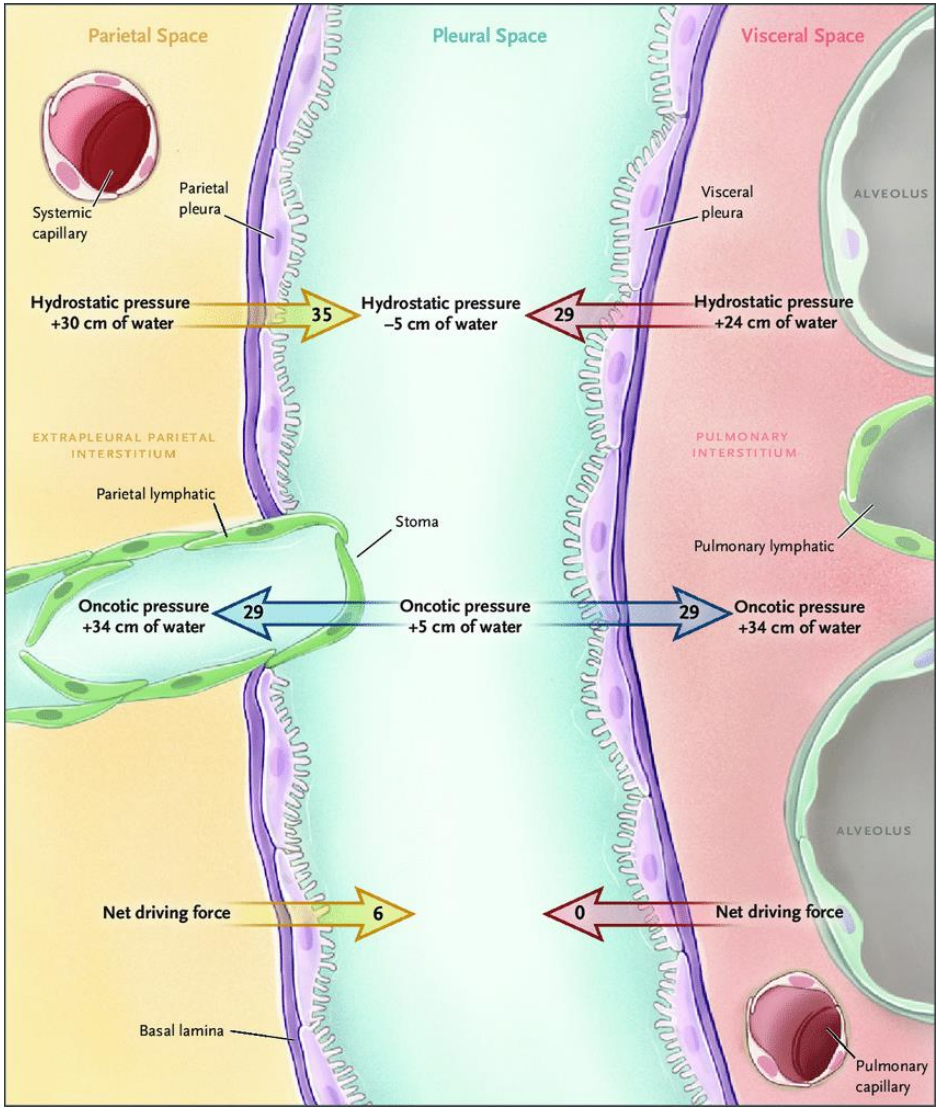
- None

Outline

- Normal pleural anatomy and function
- Evaluating pleural effusions
  - Imaging
  - Thoracentesis
  - Pleural fluid analysis
- Management of effusions
- A few special cases
- Evaluating the exudative effusion of unknown etiology


Mesothelial cells
CT
Pleural space

Normal Pleural Anatomy



- Basal pleural fluid volume: ~2.0 ml/hr
  - Daily production: ~25 ml/day
- Drainage capacity: ~15 ml/hour
  - Daily absorption ~350 ml/day

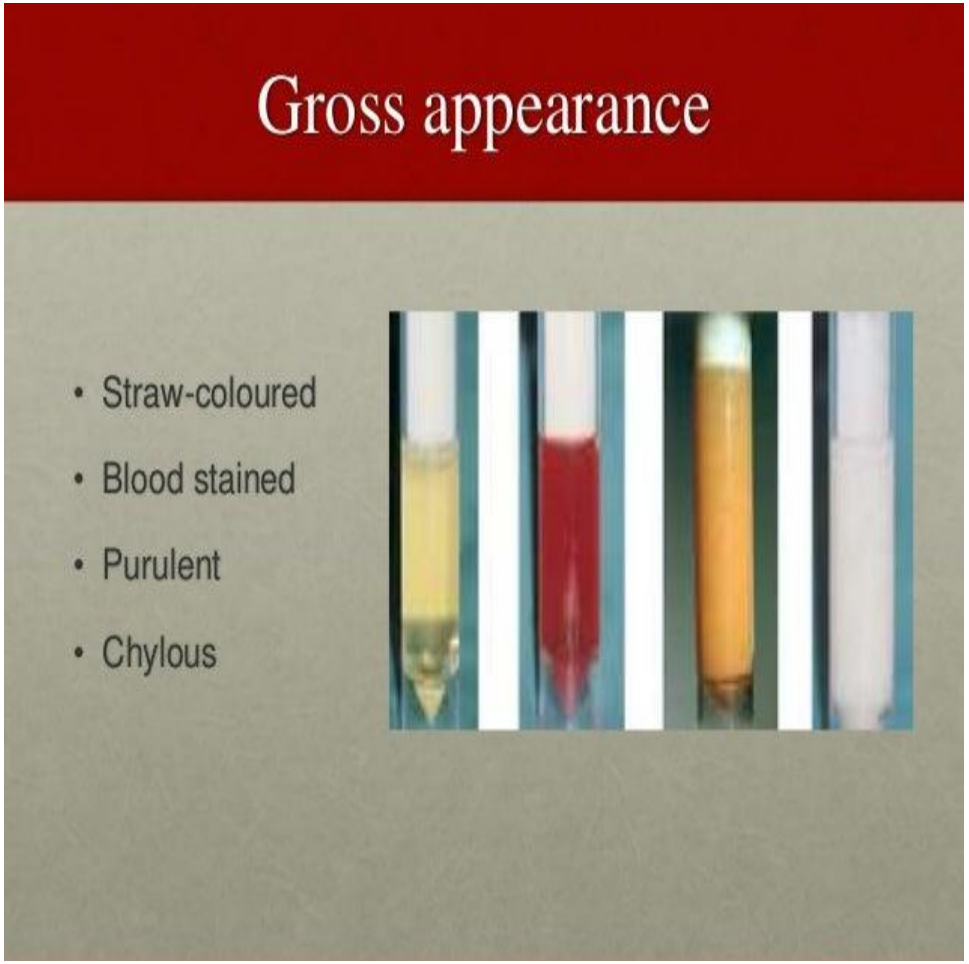
Back to the Basics:
Transudate or Exudate (Light's criteria)

- 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

*Light, RW. *Clin Chest Med* 2013; 34: 21-26

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

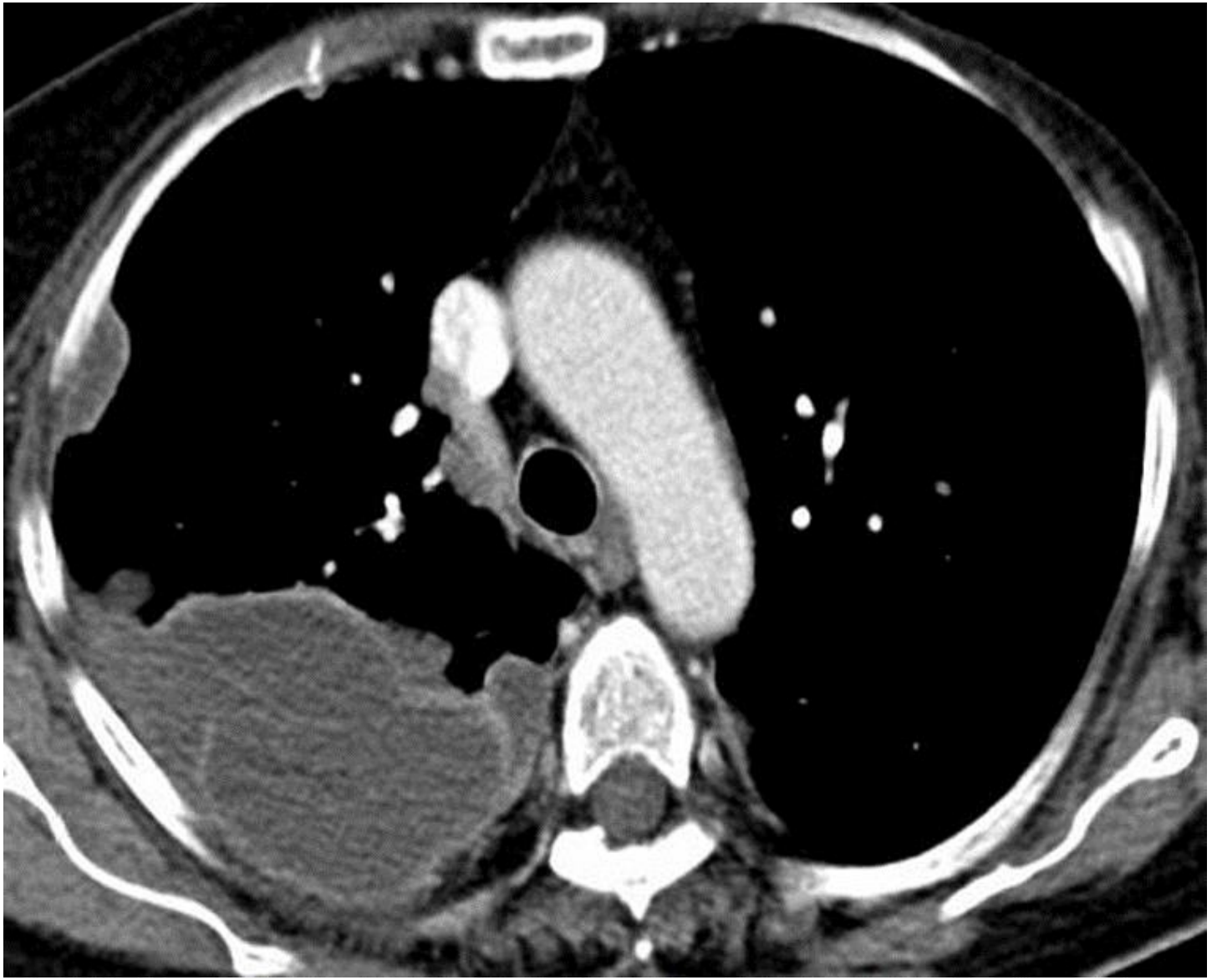
Diagnostic Evaluation of Pleural Effusions

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….

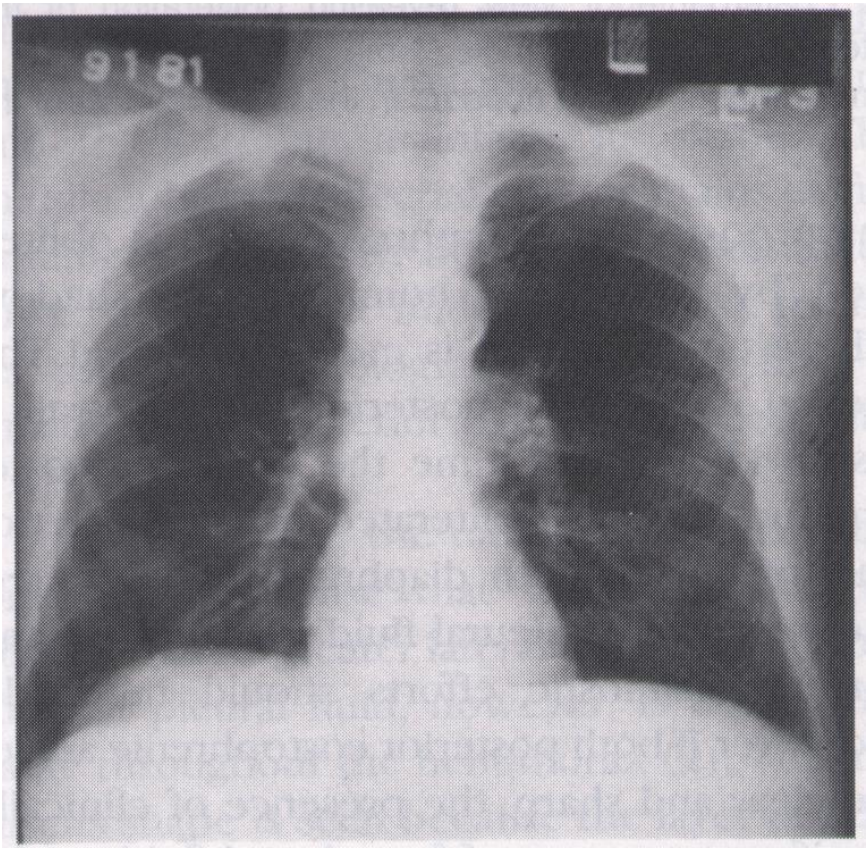
Terms

- **“Simple” Parapneumonic effusion** –free flowing
- **Loculated parapneumonic effusion** –presence of **septations** (separate compartments) within the effusion
- **Empyema** – Grossly purulent fluid in the pleural cavity, with or without positive bacterial culture.
- **“Complicated” parapneumonic effusion** –term is often used to refer to either loculated effusion or empyema.

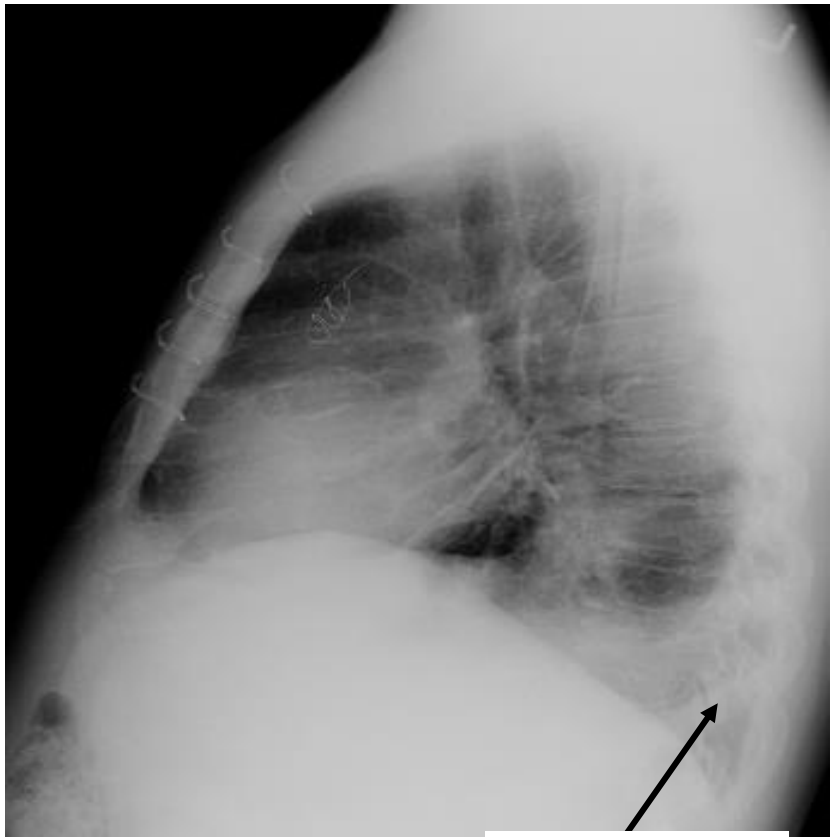


The Value of the Lateral Film

AP film



Lateral film



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

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

Feller-Kopman et al 2007 Ann Thoracic Surg:

Let’s start with a classic

- 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)
- Imaging revealed a flowing moderate-sized effusion
- Blood cultures were obtained and Antibiotics started

- 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 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

Who needs a chest tube?

- Best indication for drainage:

  pleural fluid pH < 7.2

- Presence of loculations on imaging should lower the threshold for chest tube insertion
- Low glucose(< 40 mg/dl) and high LDH > 1000 IU/L often imply complicated effusion

Note: Big chest tubes are not necessarily better then smaller ones and smaller ones cause less pain (MIST-2 trial)

Microbiology of COMMUNITY-Acquired Pleural Infections

	Community acquired	Hospital acquired
Gram positive	65.1%	51.5%
Gram negative	17.1%	37.5%
Anaerobe	17.8%	11%
Most common	Viridans strep (s. milleri most common) S. Aureus (MSSA > MRSA) Enterobacteria Klebsiella Pseudomonas	S. Aureus (MRSA > MSSA) Enterobacteria Enterococci Viridans strep Pseudomonas Klebsiella

Hassan M, et al. Eur Respir J 2019;54:1900542

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

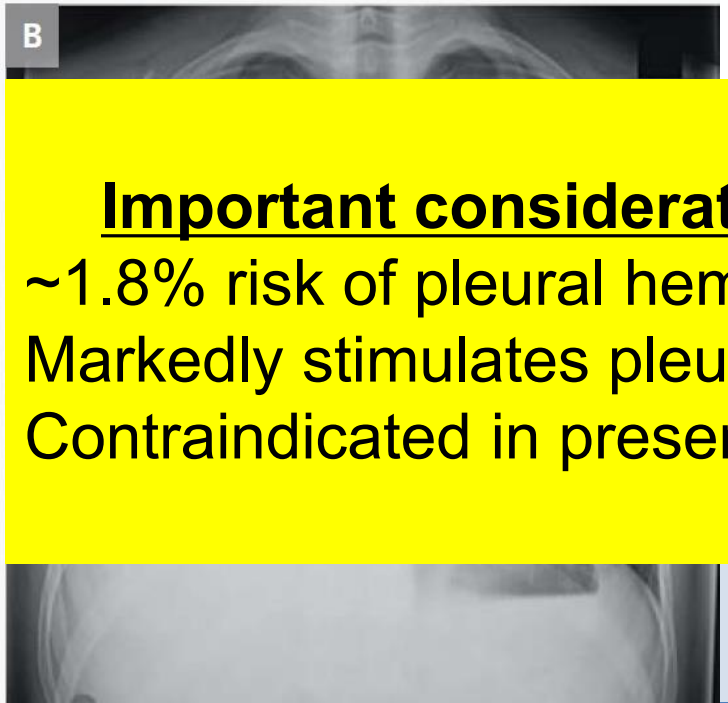
Treating Complex Parapneumonic Effusions / Empyema

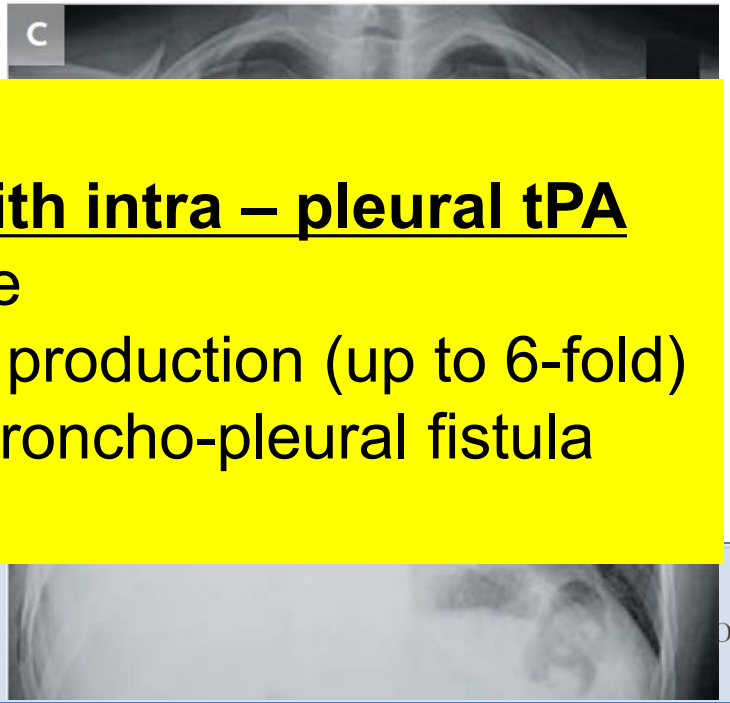
- Definitive Pleural Drainage
  - Commonly via chest tube
  - Serial thoracenteses an alternative, but not well-studied

- 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

Small Drainage Catheters + Fibrinolytic + DNA'se Treatment of Empyema (**MIST 2**)

- 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





<u>Important considerations with intra – pleural tPA</u>

~1.8% risk of pleural hemorrhage

Markedly stimulates pleural fluid production (up to 6-fold)

Contraindicated in presence of broncho-pleural fistula

Treating Complicated 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 courses up to 4-6 weeks frequently used
  - Sometimes longer courses required for atypical pathogens (e.g. actinomyces) or in cases of prolonged pleural drainage

Next Case

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

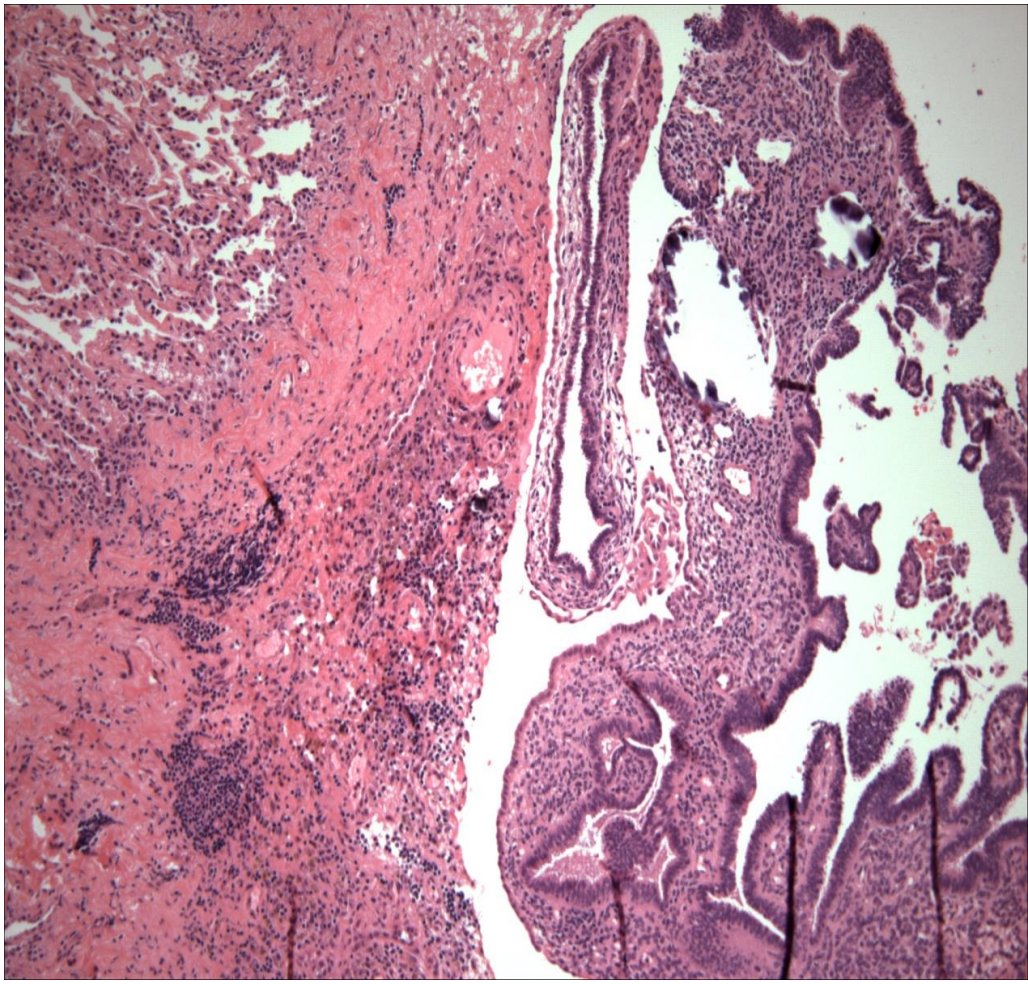
Fluid Hematocrit	Cause
<1%	Not significant
1-20% (hemorrhagic process)	Cancer>> PE>Trauma>empyema
20 – 50%	Hemorrhagic process v. Hemothorax
>50% circulating HCT	Hemothorax

Back to the case…

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

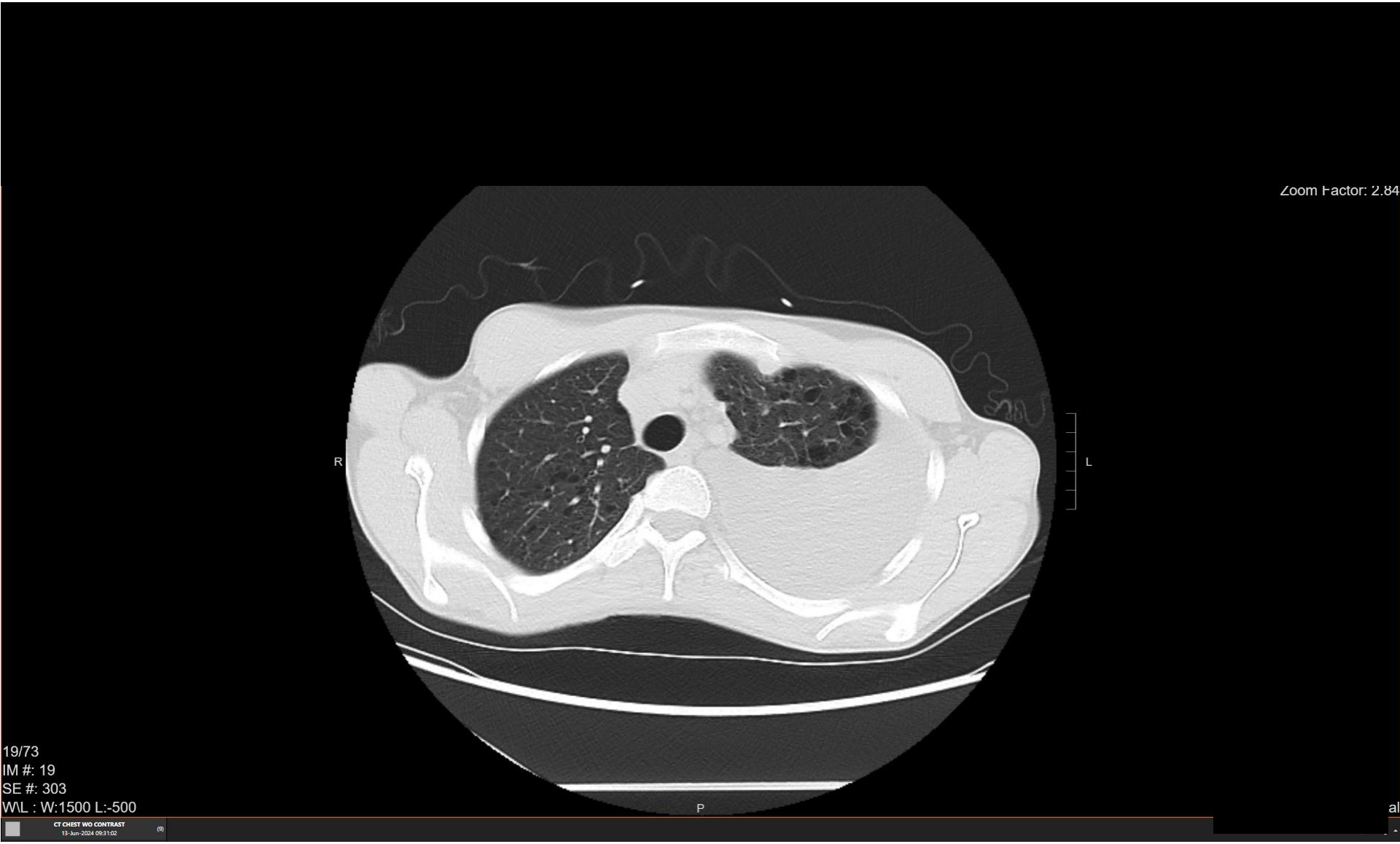
- ***Thoracic Endometriosis***

(catamenial hemothorax)



How about this one

- 26 yo man with: 3-4 months of SOB, cough, hoarseness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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)

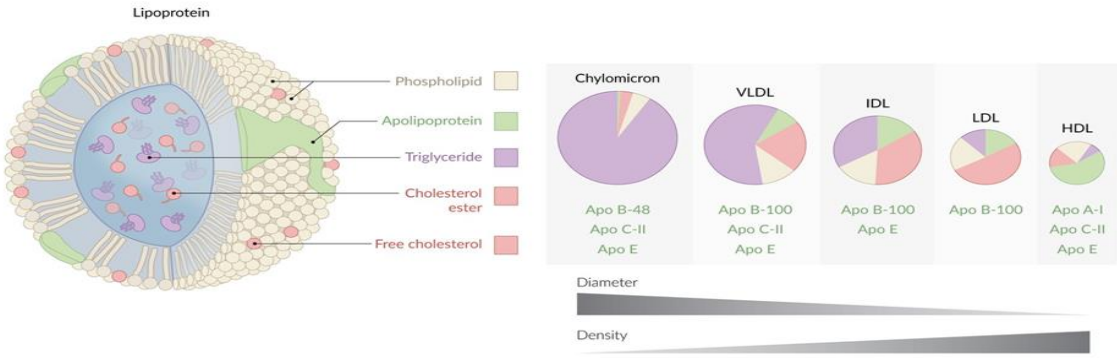
>110	50-110	<50
Chylothorax	Lipoprotein analysis	PSEUDO-Chylothorax (likely chronic exudate)

+ Chylomicrons -> CHYLOTHORAX

↓

Traumatic	Non Traumatic
Chest trauma Thoracic surgery	Lymphoma, solid tumors, chest XRT Histoplasmosis, MTB, Sarcoid Chylous ascites LAM, yellow nail syndrome, Amyloid L subclavian DVT Filariasis

Chylous vs Pseudochylous



- **Chylothorax**:

  TG_{fluid} > 110mg/dL

  $TG_{fluid} > TG_{serum}$

  $Cholesterol_{fluid} < 200$ mg/dL

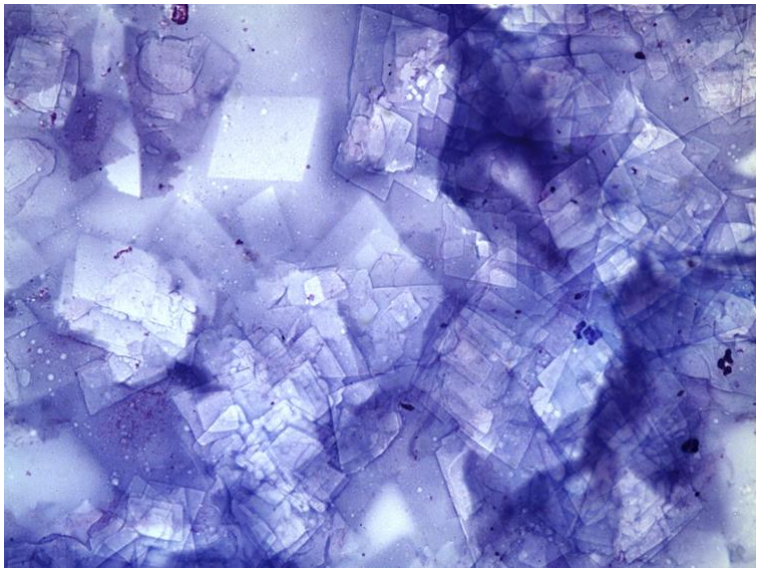
  + <u>chylomicrons</u>

- **Pseudo - Chylothorax**:

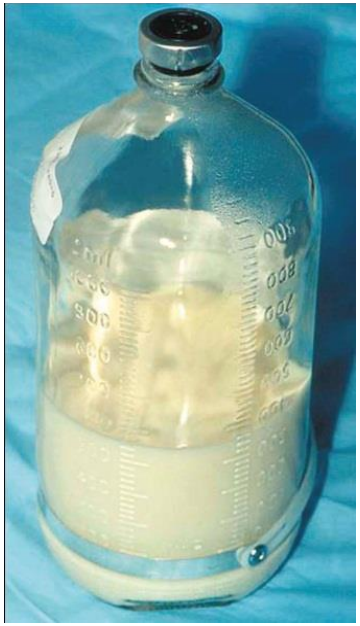
  Cholesterol > 250 mg/dL

  + cholesterol crystals (rhomboid)

  TG_{fluid} LOW



Chyle Loss Increases Mortality



Fat

Vitamins
A, D, E, K

Malnutrition

Proteins
Immunoglobulins

Lymphocytes

Immunosuppression

17-35% mortality
(limited data)

4.5-fold ↑ risk
of death in
surgical patients

Paul et al. *J Thorac Cardiovasc Surg.* 1985 Feb;89(2):221-7.
Shah et al. *Ann Thorac Surg.* 2012 Mar;93(3):897-903.

Management

↓ Chyle Flow

No short- or long-chain TG intake
Octreotide or Somatostatin

Remove Chyle

Thoracentesis
Tube Thoracostomy
Pleuroperitoneal Shunt
Pleurovenous Shunt

Maintain Nutrition

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

Close Chyle Leak

Pleurodesis
Duct Embolization
Surgical Duct Ligation

Special Case

- 74-year-old man with a history of CAD, DVT, aortic aneurysm, hyperlipidemia, basal cell skin cancer, who developed an abnormal sensation in his left chest 2 months ago was found to have a small left pleural effusion. Pleural fluid analysis:
- pH 7.46
- Total protein 4.3
- LDH 232

Pleural fluid Color, Fluid Red

Total Nucleated Cells, **2,412 High**

Neutrophil Count, Body Fluid %

% **22**

Lymphocytes, Body Fluid %

% **57**

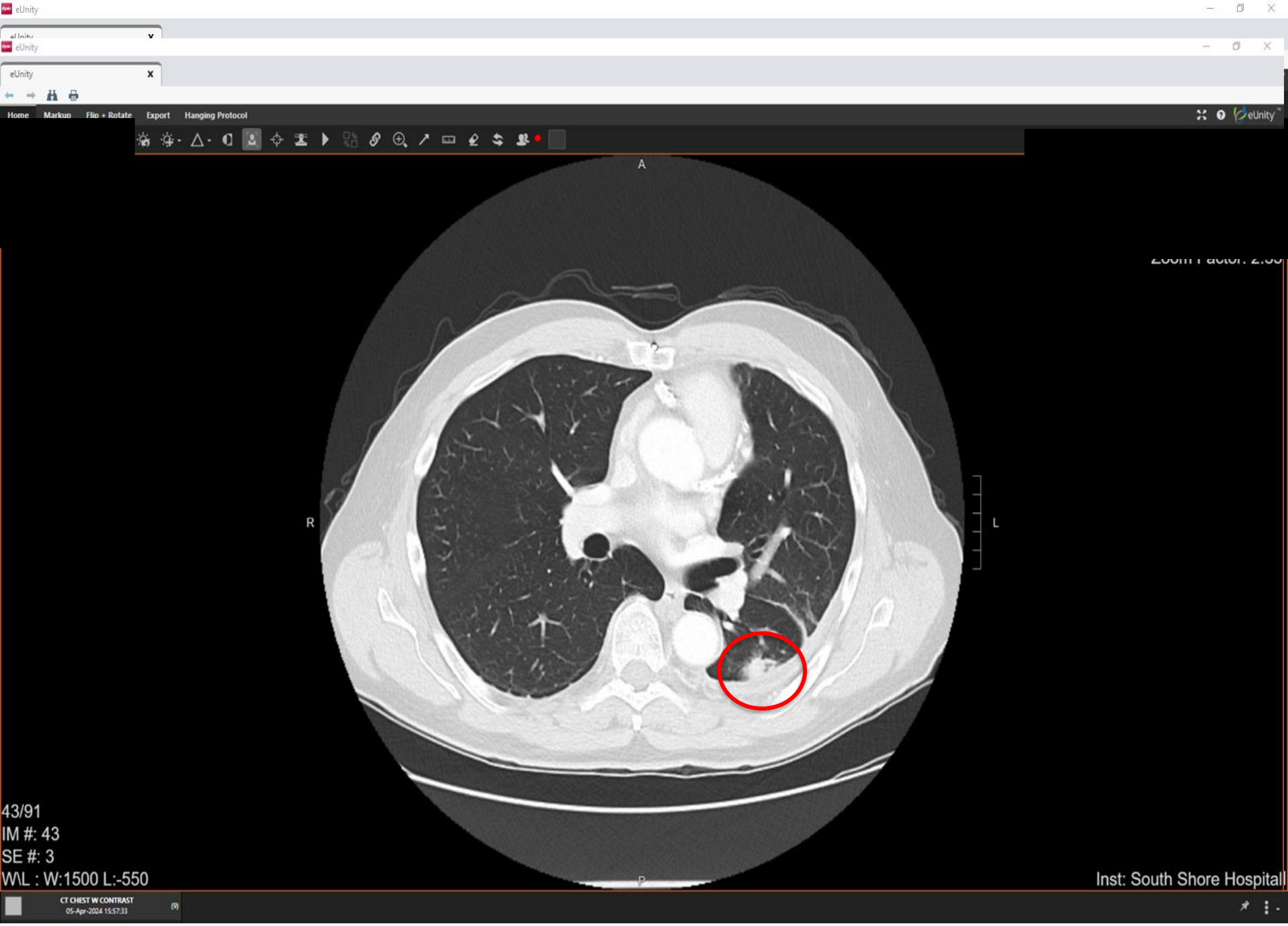
Mono+Macro, Body Fluid %

% **12**

Eosinophils, Body Fluid %

% **9**

RBC, Body Fluid 0 - 50000 /mm3 **69,000** High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Benign asbestos pleural effusion (BAPE)

- Small, unilateral effusion develop years before the asbestos related ILD
- Usually associated with other signs of asbestos exposure, i.e. 92% concomitant pleural plaques
- 1/3 have increased pleural eosinophils
- Exudative, sometimes serosanguinous or even bloody
- Usually resolve spontaneously

Final case

- 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

- Presents 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

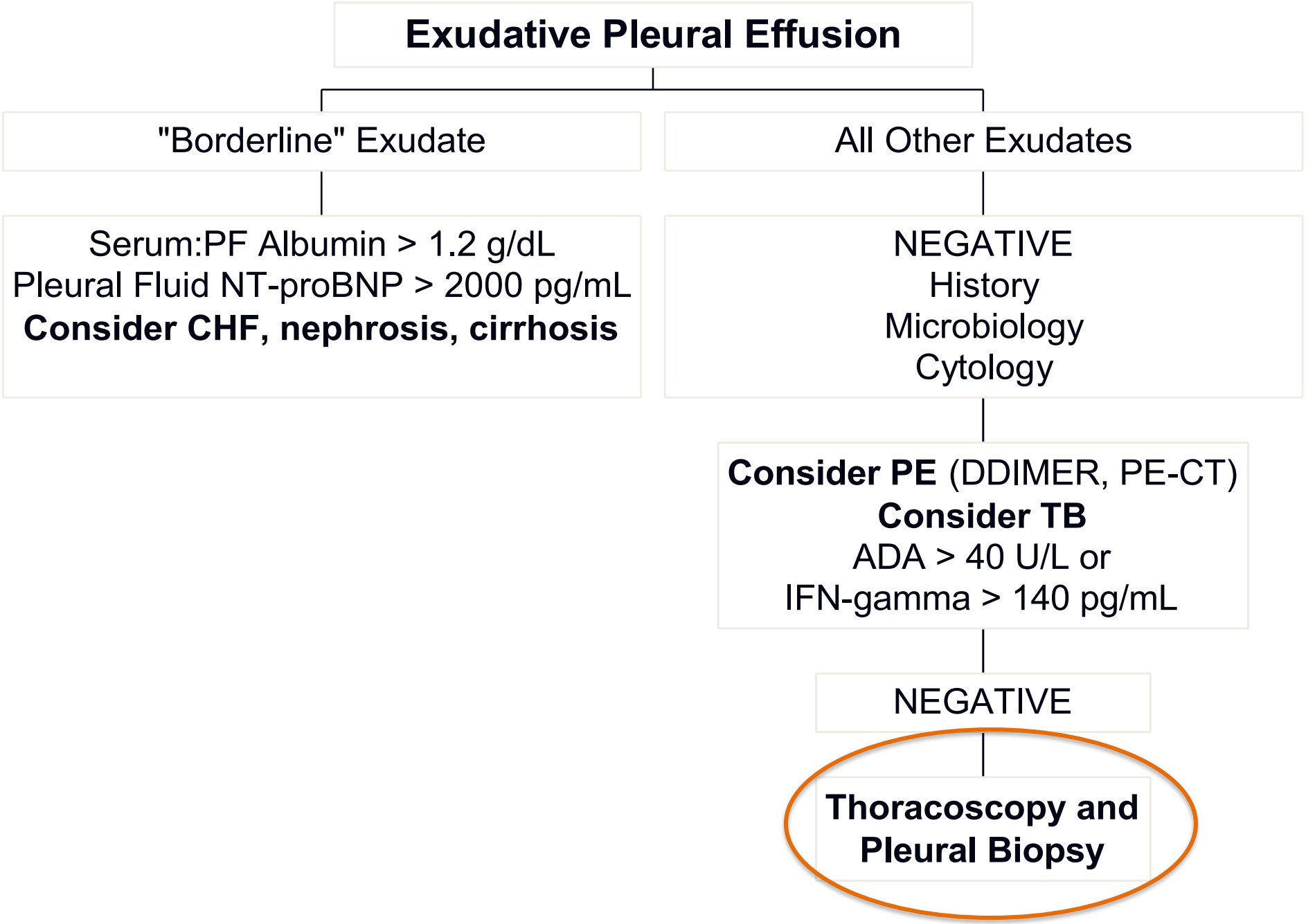
- Labs:
  - Serum: LDH 229, Total Protein 6.5, Albumin 3.7
  - Fluid: LDH 226, Total Protein 4.1, Albumin 2.7
    pH 7.6, Glucose 208, Amylase 12
  - Fluid: ADA 3.1 (usually > 40 U/L in tuberculous pleural effusions)

- 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

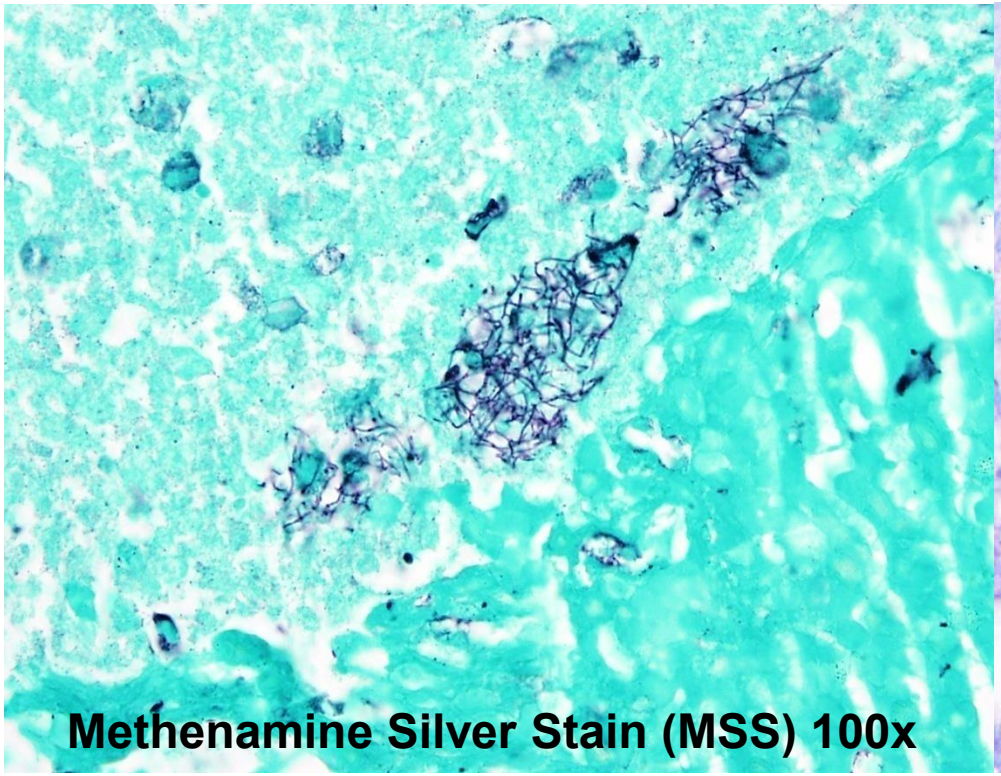
- Most undiagnosed exudates are from:
  - Malignancy (including mesothelioma)
  - Chronic empyema (including atypical organisms)
  - Tuberculosis
  - Rheumatoid Arthritis / inflammatory
  - Pulmonary Embolus
  - “Diuresed” CHF


Exudative Pleural Effusion
"Borderline" Exudate
All Other Exudates
Serum:PF Albumin > 1.2 g/dL
Pleural Fluid NT-proBNP > 2000 pg/mL
Consider CHF, nephrosis, cirrhosis
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

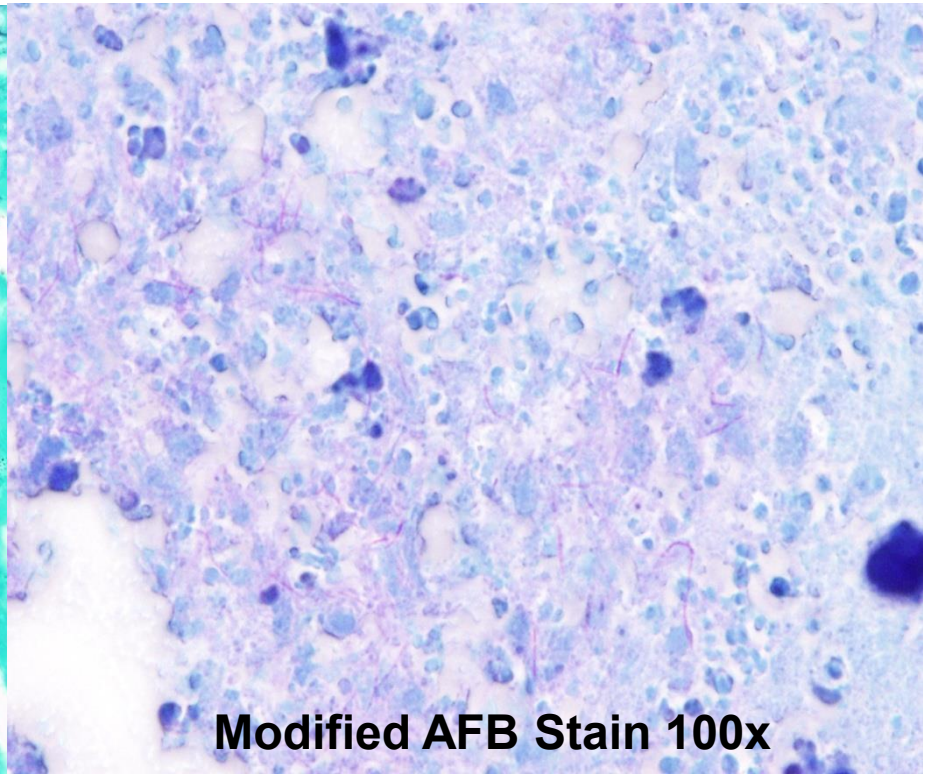
Back to the case… evaluation for Infection

- 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

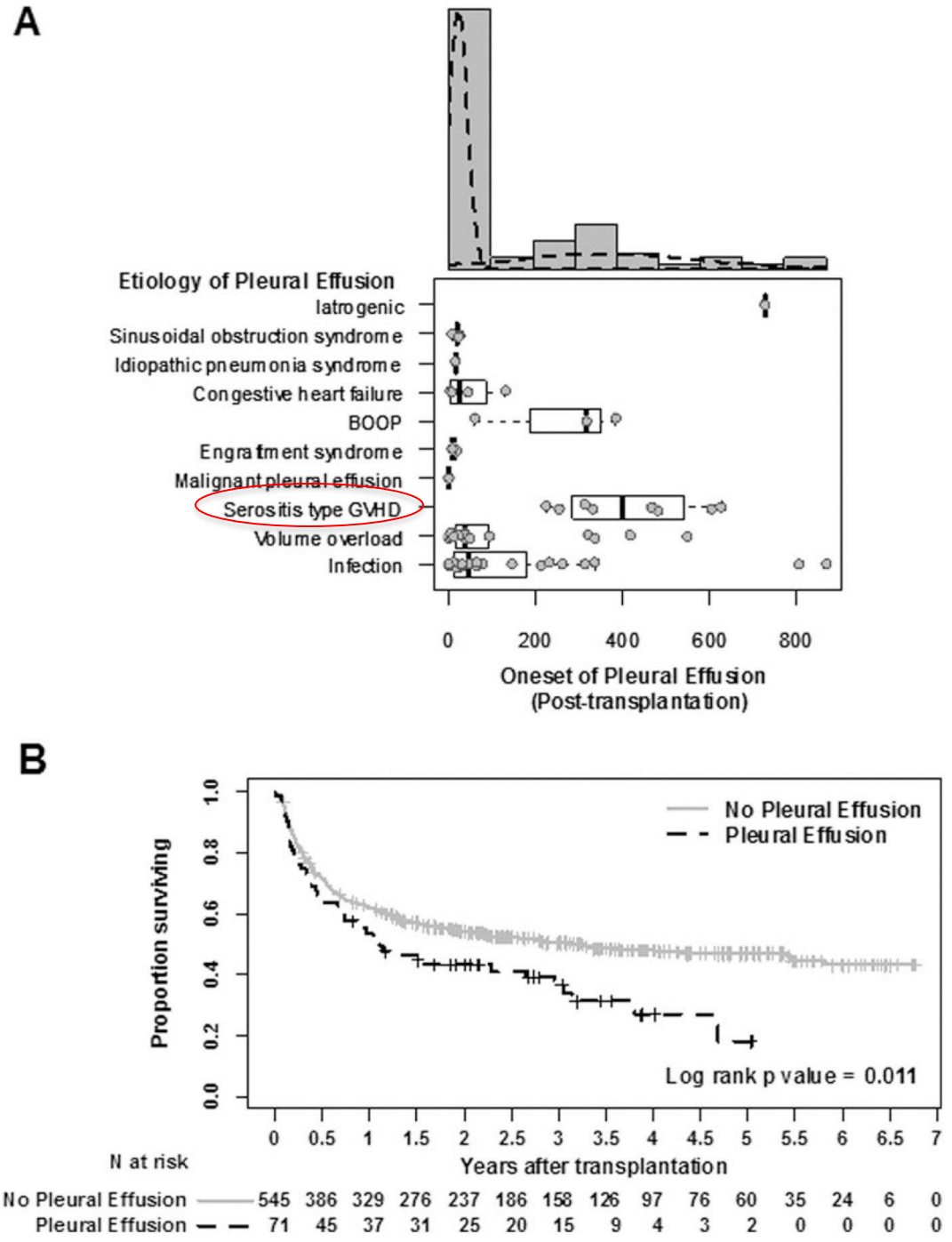


Methenamine Silver Stain (MSS) 100x



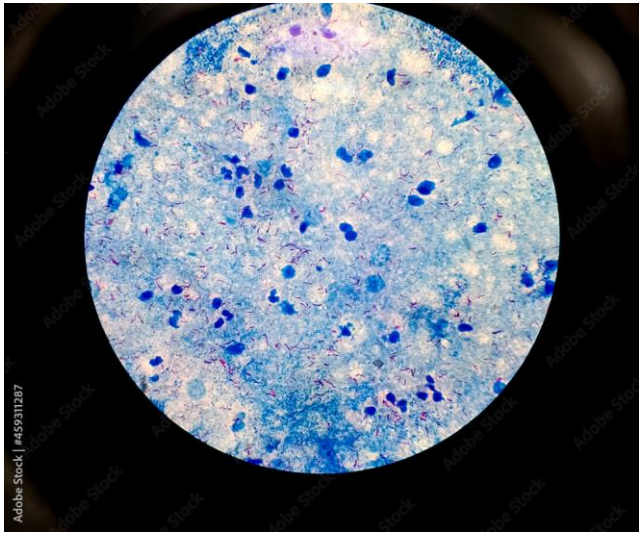
Modified AFB Stain 100x

The BMT patient



Am J Hematol. 2016 September ; 91(9): E341–E347.
doi:10.1002/ajh.24435.

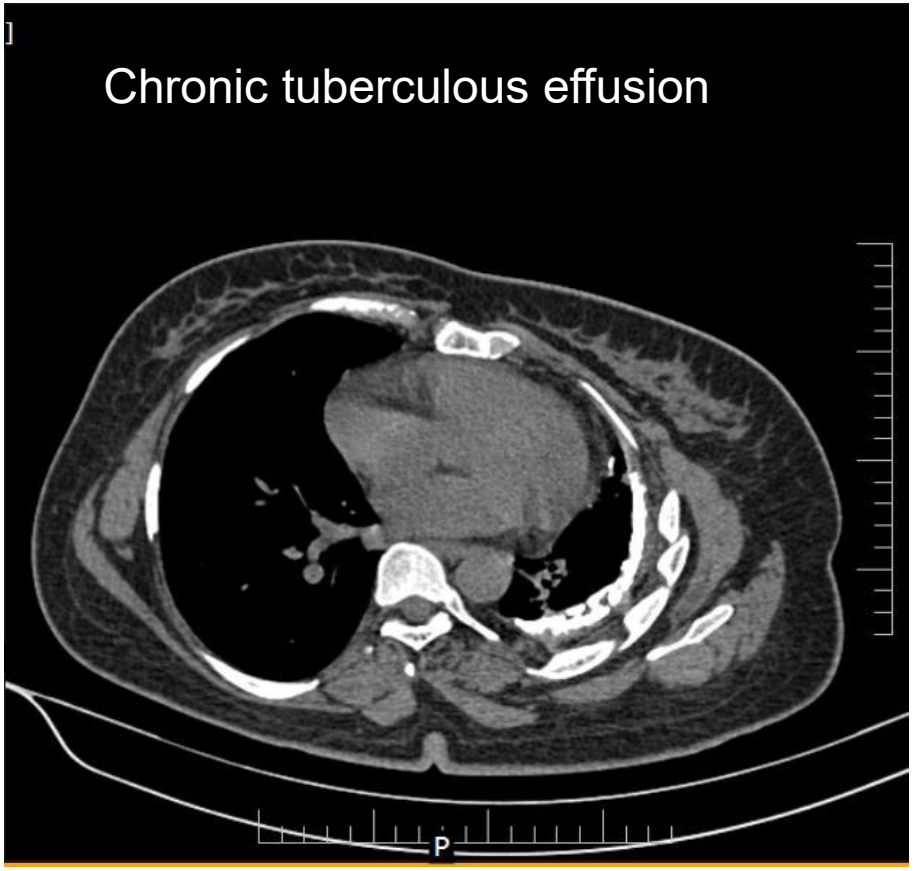
Special Case



Tuberculous pleural effusion

- In adults, occurs most commonly with reactivation although can occur with primary infection.
- Definitive diagnosis by identification of mTB in pleural fluid or pleural biopsy
- Presumptive diagnosis if high suspicion and
  - Pleural fluid lymphocytic-to-neutrophil ratio >0.75 and pleural fluid adenosine deaminase (ADA) >40 units/L, or
  - demonstration of one or more caseating granulomas on pleural biopsy

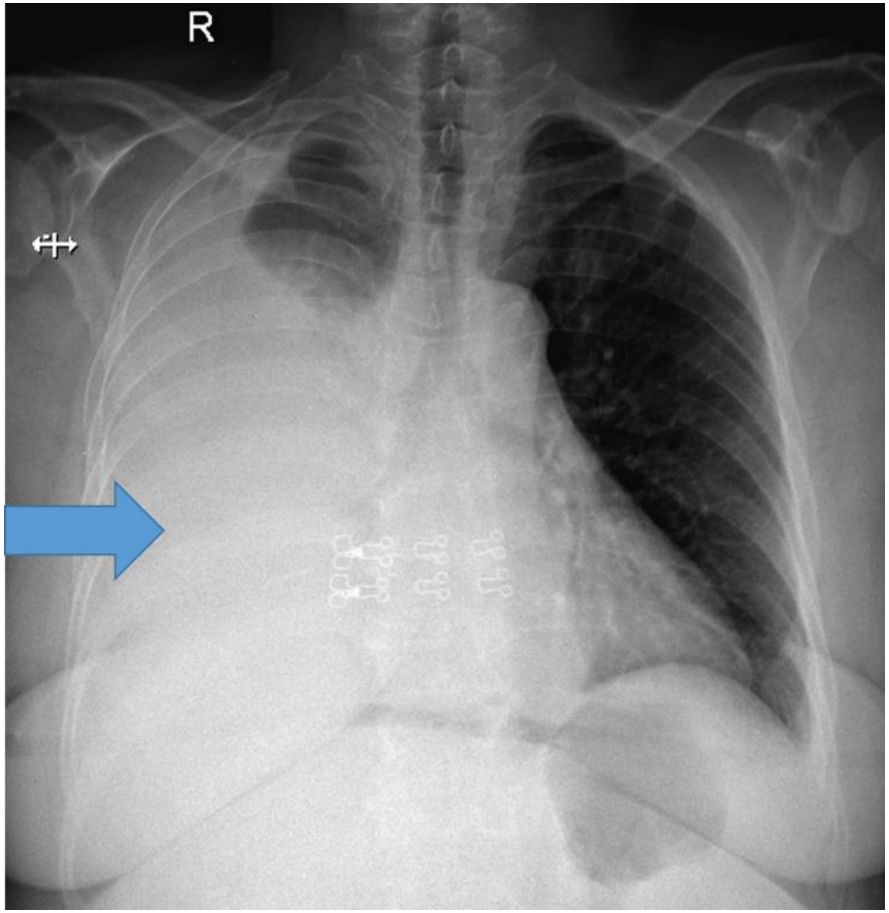
Typically, pH < 7.4, glucose usually 60-100 but sometimes lower, and few mesothelial cells are seen. Eosinophils may be present but usually lymphocytes are the dominant cell.



Special Case

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*



Key Summary Points

- Empyema
  - Chest tube + fibrinolytic therapy a good treatment option, but initial VATS reasonable for low-risk surgical patients with complex empyema
- Exudative Pleural Effusions of Unclear Etiology
  - Determine whether fluid is a “pseudo-exudate” (i.e. borderline transudate)
  - Use diagnostic clues from the history, physical and associated imaging findings (e.g. infiltrate, mass, lymphadenopathy)
  - Pleural biopsy may be necessary
- Hepatic Hydrothorax
  - Salvage therapy with TIPS or indwelling pleural catheter reasonable in select cases
- Chylothorax
  - Malnutrition and lymphopenia lead to significant morbidity and mortality
- TB
  - Suspicion plus either identification of mTB in fluid or pleural biopsy; or high pl ADA

Further Reading

1. Light, RW. Pleural Effusion. *N Engl J Med* 2002; 346: 1971
2. Light, RW. The Light Criteria The Beginning and Why they are Useful 40 Years Later. *Clin Chest Med* 2013; 34: 21-26
3. NM Rahman, et al. Intrapleural Use of Tissue Plasminogen Activator and DNase in Pleural Infection. N Engl J Med 2011;365:518-526
4. McGrath EE and Anderson PB. Diagnosis of Pleural Effusion: A systematic approach. *Am J Critical Care* 2011; 20: 119
5. Porcel Jose M. Pearls and myths in pleural fluid analysis. *Respirology* 2011; 16: 44