Pleural Fluid Analysis in Infectious Disease

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Pleural effusions provide numerous clues to the diagnosis of certain disease processes. Much information can be gleaned at the bedside. Simple laboratory tests provide further information.

Pleural effusions often provide the first evidence of underlying pleural or systemic disease. Early determination of the pleural fluid composition will help in the diagnosis of the disease and prevent permanent lung dysfunction.[1,2] In this article we review and consolidate the information needed by the clinician to establish the cause of a pleural effusion.

PHYSICAL FINDINGS

Several physical findings are consistent with a pleural effusion. Chest examination may reveal increased respiratory rate, increased respiratory effort, and decreased depth of breathing, while palpation may yield characteristic decreased respiratory excursion and decreased vocal fremitus. Dullness to percussion and the auscultatory findings of decreased, adventitial, or absent breath sounds are additional clues to the diagnosis of pulmonary effusion (*Table 1*).[2,3]

LOCATION OF EFFUSION

The location of a pleural effusion yields important diagnostic information. Bilateral pleural effusions are commonly due to congestive heart failure, nephrotic syndrome, pleural metastatic disease, collagen vascular disease, myxedema, and mediastinal irradiation—not to infection. Pleural effusions located on the right side are commonly caused by right-sided subphrenic abscess/ascites, hepatic cirrhosis, or pancreatitis (secondary to biliary tract disease). Congestive heart failure usually is seen as a bilateral pleural effusion, but not uncommonly as an isolated right-sided pleural effusion. Pleural effusions that present in the left pleural space may be secondary to esophageal perforation, Dressler's syndrome, or pancreatitis due to nonbiliary disease. Several other infectious causes of pleural effusions are listed in *Table 2*.[3-5]

TRANSUDATES VS EXUDATES

Although pulmonary transudates have three basic causes, many authorities separate pleural effusions into transudates or exudates. Since the cause of a pulmonary transudate is recognizable on physical examination (eg, heart failure, cirrhosis, nephrosis) *before* thoracentesis is performed, classification of a pulmonary effusion as a

Table 1
Physical Findings Associated With Pleural Effusions

Inspection
Increased respiratory rate
Increased respiratory effort

Palpation
Decreased respiratory excursion
Decreased vocal fremitus
Large pleural effusion may shift trachea to opposite side

Percussion
Dullness

Auscultation
Decreased breath sounds
Adventitial breath sounds
Absence of breath sounds

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Table 2
Diagnosis by Location or Exclusion of Pleural Effusions

Left-Sided Pleural Effusions

Noninfectious Causes	Infectious Causes
Systemic lupus erythematosus	Group A streptococci/ *S pneumoniae*
Esophageal perforation	*H influenzae*
Dressler's syndrome	*Klebsiella* sp
Pancreatitis (secondary to nonbiliary disease)	*Mycoplasma* sp
Pleural reactions to asbestosis (benign pleural plaques, malignant mesothelioma, benign exudative effusion)	Fungal (coccidioidomycosis, histoplasmosis
Pulmonary infarction	Tuberculosis (primary not reactivation)
Left-sided chest trauma	Subphrenic abscess
Tuberous sclerosis	
Left-sided chest irradiation	
Malignancy (bronchogenic carcinoma most common)	
Histiocytosis X	
Whipple's disease	
Familial Mediterranean fever	

Bilateral Pleural Effusions

Noninfectious Causes	Infectious Causes
Congestive heart failure	None
Nephrotic syndrome	Bilateral subphrenic abscess
Cirrhosis/ascites	
Pleural metastatic disease from extrathoracic primary malignancy†	
Systemic lupus erythematosus	
Rheumatoid arthritis	
Myxedema	
Mediastinal irradiation	
Yellow-nail syndrome	

Right-Sided Pleural Effusions

Noninfectious Causes	Infectious Causes
Congestive heart failure	Pleural amebiasis
Hepatic cirrhosis	Group A streptococci/ *Streptococcus pneumoniae*★
Meig's syndrome	*Haemophilus influenzae*
Pancreatitis (secondary to biliary tract disease)	*Klebsiella* sp
Pulmonary reactions to asbestosis (benign pleural plaques, malignant mesothelioma, benign exudative effusion)	*Mycoplasma/Legionella*
Pulmonary infarction	Fungal (coccidioidomycosis, histoplasmosis)
Right-sided chest trauma	Tuberculosis (primary not reactivation)
Tuberous sclerosis	Subphrenic abscess
Right-sided chest irradiation	
Malignancy (bronchogenic carcinoma most common)	
Histiocytosis X	
Whipple's disease	
Systemic lupus erythematosus	
Familial Mediterranean fever	

Pleural Effusions Uncommon

Noninfectious Causes	Infectious Causes
Sarcoidosis	Viral pneumonias
Adult respiratory distress syndromes	*Pneumocystis carinii*
Pulmonary hemorrhagic syndromes	Fungal pneumonias (*Cryptococcus, Aspergillus, Sporothrix* sp)
Pulmonary vasculitis syndromes	Reactivation tuberculosis

★Radiographically significant pleural effusions are uncommon with *S pneumoniae, Mycoplasma* and *Legionella* sp, pulmonary Q fever, and pulmonary tularemia.

†Bronchogenic carcinoma is a rare cause of bilateral pleural effusion. Right-sided effusions are usually larger than left.

transudate or exudate is not necessary and provides no useful diagnostic information. All disease processes except congestive heart failure, nephrosis, and cirrhosis produce exudates.[2]

GROSS CHARACTERISTICS

The etiology of a pleural effusion may be determined by gross examination of the pleural fluid at the patient's bedside. The color and consistency of the fluid suggest the diagnosis (*Table 3*).[1-4,6,7]

LABORATORY EVALUATION

Pleural fluid cell counts and pH level are helpful in characterizing effusions. A red blood cell concentration of

>100,000/μL commonly is secondary to trauma, malignancy, or pulmonary infarction, whereas a few red blood cells may suggest tuberculosis. The initial finding of a predominance of polymorphonuclear leukocytes is nonspecific, but if subsequent thoracentesis yields a predominance of lymphocytes, a diagnosis of tuberculosis must be considered. The determination of pleural fluid pH is quite useful in certain differential diagnoses, eg, carcinoma vs tuberculosis. If the pH is <6, esophageal perforation is the most likely cause (*Table 4*).[1,3,4,6,7] Specific diseases are suggested by the presence of malignant cells (lung, breast, stomach, or ovarian carcinomas) or eosinophils (pulmonary parasitic diseases or periarteritis nodosa).

Other pleural fluid indices include decreased glucose and C_3 levels, rheumatoid factor, hyaluronic acid, and amylase. A decreased C_3 level can limit the differential diagnosis to systemic lupus erythematosus, rheumatoid arthritis, or infection. An increased level of hyaluronic acid is a common finding in effusions secondary to malignant mesothelioma.

A finding of pleural fluid and peripheral blood

Table 3
Gross Characteristics of Exudative Effusions Associated With Various Diseases

Characteristic	Disease
Purulent	Empyema
Feculant odor	Empyema secondary to anaerobic organisms
Bloody	Tularemic pneumonia, malignancy, pulmonary infarction, trauma, hemophilia, dissecting aortic aneurysm, coagulation disorder
Turbid, greenish yellow	Rheumatoid arthritis
Very viscous	Mesothelioma
Anchovy-paste (chocolate-brown)	Pleural amebiasis
White, milky	Chylothorax (damage or obstruction to thoracic duct)
Satiny	Pseudochylous (chronic effusion of any cause, eg, cyst fluid, rheumatoid disease, tuberculosis, myxedema)

Table 4
Pleural Fluid Cells and pH Associated With Various Diseases

WBC, >10,000/μL	RBC, >10,000/μL
Pneumonia	Trauma
Empyema	Tularemia
Pancreatitis	Malignancy
Pulmonary infarction	Tuberculosis
Collagen vascular disease	Pulmonary infarction
Malignancy	
Eosinophilia†‡	**PMN Predominance***
Postoperative effusion	Early tuberculosis (primary)
Viral pneumonia (*Varicella* sp)	Bacterial pneumonia
Closed chest trauma	Pancreatitis
Congestive heart failure	Pulmonary infarction
Fungal infection (coccidiodomycosis, histoplasmosis)	Peritonitis (sympathetic effusion)
Pulmonary hypersensitivity syndromes	**Lymphocyte Predominance**
Polyarteritis nodosa	Late tuberculosis (primary)
Mesothelioma	Malignancy
Pneumothorax	Rheumatoid arthritis
Postpneumonic effusion	Systemic lupus erythematosus
Pulmonary infarction	Lymphomas
Pulmonary parasitic infection	**Pleural Fluid pH**
Hodgkin's lymphoma	<6, Esophageal perforation
Q fever (80% eosinophils)	<7.3, Tuberculosis, empyema, rheumatoid arthritis, systemic lupus erythematosus
	>7.3, Malignancy

*50% Polymorphonuclear (PMN) leukocytes argues against carcinoma and the three causes of transudates.
†Significant pleural fluid eosinophilia argue strongly against a diagnosis of tuberculosis, malignancy (except for lymphoma).
‡Concurrent peripheral and pleural eosinophilia should suggest Loffler's syndrome, lymphoma, malignancy, pleuropulmonary hydatid cyst disease, tropical eosinophilia, or polyarteritis nodosa.

Table 5
Pleural Fluid Chemistries

Decreased C_3	Increased Rheumatoid Factor
Systemic lupus erythematosus	Rheumatoid arthritis
Rheumatoid arthritis	Tuberculosis
Infection	Pneumonia
	Malignancy
Increased Hyaluronic Acid	**Decreased Glucose**
Malignant mesothelioma	Tuberculosis
	Infection
	Malignancy
	Rheumatoid arthritis
Increased Amylase	Systemic lupus erythematosus (slightly)
Pancreatitis	
Esophageal perforation*	
Malignancy	

*≥10,000 Somogyi U/dL

Table 6
Pleural Effusion Profiles in Various Diseases

Tuberculosis	Malignancy
WBC, <5,000/μL	WBC, >10,000/μL
<1% mesothelial cells	RBC, >100,000/μL
RBC, <10,000/μL	↑LDH_2/LDH_5
Lymphocyte predominance	pH >7.3
pH <7.3	↓α_2-globulins
No eosinophilia	↑Rheumatoid factor
↑Rheumatoid factor	↓Glucose
↓↓Glucose	↓Amylase
Pleural biopsy/culture positive for AFB	Cytology positive for malignant cells
Empyema	**Rheumatoid Arthritis**
Purulent	Turbid, greenish yellow
Feculant odor secondary to anaerobic organisms	WBC, >10,000/μL
WBC >50,000/μL	pH <7.3
PMN predominance	↓C_3
pH <7.3	↑Rheumatoid factor
	↓↓Glucose
	↑↑Protein
	Degenerated PMN and amorphous cellular debris
Systemic Lupus Erythematosus	**Mesothelioma**
↑PMN/lymphocytes	Very viscous (clear or cloudy)
No RBCs	Eosinophilia
Normal/glucose	pH >7.3
↓C_3	

AFB = acid-fast bacillus; PMN = polymorphonuclear leukocytes; RBC = red blood cells; WBC = white blood cells; ↑= increase; ↓= decrease.

eosinophilia may suggest Löffler's syndrome, polyarteritis nodosa, tropical eosinophilia, and hydatid cyst. Pleural fluid rheumatoid factor is found in patients with rheumatoid arthritis, tuberculosis, pneumonia, and malignancy, and an increased amylase level is seen with pancreatitis, esophageal perforation, and salivary gland or ovarian malignancies (*Table 5*).[1,3,4,6-8]

In *Table 6* are given some commonly encountered pleural effusion profiles, namely, tuberculosis, malignancy, empyema, mesothelioma, systemic lupus erythematosus, and rheumatoid arthritis.

CONCLUSION

Pleural effusions should be viewed as clues to a disease process. As diagnostic clues, pleural effusion fluid analyses must be interpreted in the clinical context and not as isolated laboratory findings. For example, the presence of clubbing in an elderly man with a unilateral pleural effusion would strongly favor a differential diagnosis of carcinoma vs tuberculosis, taking precedence over most pleural findings. It is important that clinicians examine pleural fluid analysis results that are diagnostically helpful and eliminate the unnecessary differentiation of exudates and transudates. □

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