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Diagnostic Significance of Quantiferon TB Gold in Tuberculous Pleural Effusion

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By

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Aim of the Work

The aim of this study is to evaluate the efficacy of Quantiferon TB Gold in diagnosing tuberculous pleural effusion.

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ADA	**:**	Adenosine deaminase.
ARDS	**:**	Acute respiratory distress syndrome.
CD	**:**	Cluster of differentiation.
CFP-10	**:**	Culture filtrate protein 10.
CHF	**:**	Congestive heart failure.
CR3	**:**	Complement receptor 3.
CT	**:**	Computed tomography.
ELISA	**:**	Enzyme linked immunosorbent assay.
EPTB	**:**	Extra pulmonary tuberculosis.
ESAT-6	**:**	Early secretory antigenic target-6.
HCW	**:**	Health care workers.
HIV	**:**	Human immunodeficiency virus.
IGRAS	**:**	Interferon gamma release assays.
IL	**:**	Interleukin.
INFδ	**:**	Interfeone gamma.
LDH	**:**	Lactate de hydrogenase enzyme.
NK	**:**	Natural killer.
PBMCs	**:**	Peripheral blood mononuclear cells.
PPD	**:**	Purifed protein derivative.

QFN-TB : Quantiferon-TB Gold-test.

QFT-G-IT : Quantiferon-TB Gold in tube method.

TACO : Tryptophan aspirate coat protein.

TB : Tuberculosis.

TLR : Toll like receptor.

TST : Tuberculin skin test.

Chapter (I)

Pleural Effusion

Anatomy of the Pleura:

The pleura is the serous membrane that covers the lung parenchyma, the mediastinum, the diaphragm, and the rib cage. This structure is divided into the visceral pleura and the parietal pleura. The visceral pleura covers the lung parenchyma, not only at its points of contact with the chest wall, diaphragm, and mediastinum but also in the inter-lobar fissures. The parietal pleura lines the inside of the thoracic cavities. In accordance with the intrathoracic surfaces that it lines, it is subdivided into the costal, mediastinal, and diaphragmatic parietal pleura ***(Light 2007)***.

A film of fluid (pleural fluid) is normally present between the parietal and the visceral pleura. This thin layer of fluid acts as a lubricant and allows the visceral pleura covering the lung to slide along the parietal pleura lining the thoracic cavity during respiratory movements. The space, or potential space, between the two layers of pleura is designated as the pleural space ***(Light, 2007)***.

The normal pleural space is approximately 18 to 20 mm in width, although it widens at its most dependent areas ***(Albertine et al., 1991)***.

The pleural membranes do not touch each other and that the pleural space

is a real, not a potential, space, it is likely that the primary function of the pleural membranes is to allow extensive movement of the lung relative to the chest wall. If the lung adhered directly to the chest wall, its expansion and deflation would be more limited ***(Deschamps and Rodarte, 1988)***.

Pathogenesis of Pleural Effusions:

Pleural fluid accumulates when the rate of pleural fluid formation exceeds the rate of pleural fluid absorption. The main factors that lead to increased pleural fluid formation or decreased pleural fluid absorption are tabulated in Table (A). Normally, a small amount (0.01 mL/kg/hour) of fluid constantly enters the pleural space from the capillaries in the parietal pleura. Almost all of this fluid is removed by the lymphatics in the parietal pleura, which have a capacity to remove at least 0.20 mL/kg/hour ***(Light, 2007)***.

***Table* (A): General Causes of Pleural Effusions *(Light, 2007)*.**

• ***Increased pleural fluid formation*:**
- **Increased interstitial fluid in the lung**
▪ **Left ventricular failure, pneumonia, and pulmonary embolus**
- **Increased intravascular pressure in pleura**
▪ **Right or left ventricular failure, superior vena caval syndrome**
- **Increased permeability of the capillaries in the pleura**
▪ **Pleural inflammation**
▪ **Increased levels of vascular endothelial growth factor**
- **Increased pleural fluid protein level**
- **Decreased pleural pressure**
▪ **Lung atelectasis or increased elastic recoil of the lung**
- **Increased fluid in peritoneal cavity**
▪ **Ascites or peritoneal dialysis**
- **Disruption of the thoracic duct**
- **Disruption of blood vessels in the thorax**
• ***Decreased pleural fluid absorption:***
- **Obstruction of the lymphatics draining the parietal pleura**
- **Elevation of systemic vascular pressures**
▪ **Superior vena caval syndrome or right ventricular failure**
- **Disruption of the aquaporin system in the pleura**

For pleural fluid to accumulate to form an effusion, it is likely that both the entry rate of liquid must increase and the exit rate must decrease. If only the entry rate increased, it would require a sustained rate more than 30 times normal to exceed the reserve lymphatic removal capacity; if the exit rate decreased, it would take more than a month at the normal entry rate of 12 mL/day to produce an

effusion detectable by chest radiograph thus, in the clinical setting, it is most likely that excess pleural fluid accumulates due to changes in both entry and exit rates ***(Broaddus, 2008)***.

Increased entry of fluid may result from increased filtration across systemic or pulmonary capillaries or entry of another fluid (e.g., chyle, cerebrospinal fluid [CSF], urine, intravenous fluids). Decreased exit of fluid may result from interference with lymphatic function (e.g., obstruction of the parietal pleural stomata, inhibition of lymphatic contractility, infiltration of draining parasternal lymph nodes, or elevation of the systemic venous pressure into which the lymph drains) ***(Broaddus , 2008)***.

There are few studies on the rate of removal of liquid in humans; however, decreases in lymphatic clearance have been confirmed in patients with tuberculous and malignant effusions and in those with the yellow nail syndrome, a disease of lymphatic function ***(Leckie and Tothill, 1965)***.

Pathogenesis of Transudative and Exudative Pleural Effusion:

In some cases, it is likely that the same disease process acts both to increase the entry and to decrease the exit of fluid, whereas, in other cases, different disease processes may act cooperatively to produce an effusion to determine the origin of effusions, a classic and useful distinction is between transudates and exudates ***(Runyon et al., 1979)***.

Transudates form by leakage of fluid across an intact capillary barrier owing to increases in hydrostatic pressures or decreases in osmotic pressures across that barrier. Transudates generally indicate that the pleural membranes are not themselves diseased. Exudates results from leakage of fluid and protein across an altered capillary barrier with increased permeability. The protein ratio, the lactate dehydrogenase (LDH) ratio, and the absolute pleural LDH concentration constitute Light's criteria ***(Light et al., 1972)***.

Transudates include various low-protein fluids that arise from non injured capillary beds. The majority of transudates are caused by CHF. These transudates have been shown to result from leakage of edema across normal pulmonary

capillaries into the pulmonary interstitium and then across the leaky visceral pleura into the pleural space ***(Wiener and Broaddus, 1993)***.

Other transudates, those associated with the nephrotic syndrome or atelectasis, may form because of altered pressures (osmotic or hydrostatic) across the pleural capillaries. Some transudates, usually small, may develop primarily because of an isolated decrease in exit rate ***(Broaddus, 2002)***.

Hepatic hydrothorax and effusions from peritoneal dialysis develop when fluid flows from the peritoneal space into the lower pressure pleural space across macroscopic holes in the diaphragm ***(Wong et al., 2009)***.

Finally, other very low protein fluids such as urine or CSF or intravenous liquids may find their way to the pleural space if their normal course is disrupted ***(Broaddus, 2008)***.

Exudates arise from injured capillary beds, in the lung, the pleura, or adjacent tissues. Most exudates, such as those associated with pneumonia or pulmonary embolism, probably form following lung inflammation and injury when a high-protein lung edema leaks into the pleural space. Another large category of exudates arises from pleural injury due to inflammation, infection, or malignancy. Exudates can also form when exudative liquid in the mediastinum (esophageal rupture or chylothorax), retroperitoneum (pancreatic pseudocyst), or peritoneum (ascites with spontaneous bacterial peritonitis or Meigs' syndrome) finds its way into the lower-pressure pleural space ***(Broaddus, 2008)***.

As stated, for either transudates or exudates, lymphatic obstruction may contribute to the accumulation of the effusion. Nonetheless, because lymphatic clearance does not alter the pleural fluid protein concentration, the protein concentration gives information about the formation of the fluid, not its removal ***(Broaddus, 2008)***.

***Table* (B): Etiology of Transudative Effusions *(Sahnl, 2008)*.**

- **Congestive heart failure**	**Urinothorax**
- **Cirrhosis**	**Meig's syndrome**
- **Nephrotic syndrome**	**Pulmonary embolism**
- **Peritoneal dialysis**	**Superior vena cava obstruction**

- **Myxedema**	**Hypoalbuminaemia**
- **Atelectasis(early)**	

***Table* (C): Etiology of Exudative Effusions *(Light, 2007)*.**

Parapneumonic	**Simple**
	Complicated
Tuberculosis	**Hypersensitivity reaction in hematogenous phase**
	Empyema as complication of post primary pulmonary T.B
Other infections	**Fungal**
	Parasitic
Malignant	**Metastatic disease**
	Mesothelioma
Pulmonary Embolism	
Collagen Vascular disease	**Rheumatoid arthritis**
	Systemic lupus erythematosus
	Wegener's granulomatosis
	Churg-Strauss syndrome
	Familial Mediterranean fever
Abdominal diseases	**Pancreatitis**
	Subphrenic abscess
	Postoperative
Miscellaneous	**Atelectasis**
	Acute respiratory distress syndrome, (ARDS)
	Asbestos exposure
	Hemothorax
	Chylothorax
	Cholesterol effusions
	Esophageal rupture
	Radiation therapy
	Ovarian hyperstimulation syndrome

Light Criteria for Exudative Pleural Effusion:

Transudative and exudative pleural effusions are distinguished by measuring the lactate dehydrogenase (LDH) and protein levels in the pleural fluid. Exudative pleural effusions meet at least one of the following criteria, whereas transudative pleural effusions meet none:

1. Pleural fluid protein/serum protein >0.5.
2. Pleural fluid LDH/serum LDH >0.6 .

3. Pleural fluid LDH more than two-thirds normal upper limit for serum.

The above criteria misidentify approximately 25% of transudates as exudates. If one or more of the exudative criteria are met and the patient is clinically thought to have a condition producing a transudative effusion, the difference between the albumin levels in the serum and the pleural fluid should be measured. If this gradient is greater than 12 g/L (1.2 g/dL), the exudative categorization by the above criteria can be ignored because almost all such patients have a transudative pleural effusion. If a patient has an exudative pleural effusion, the following tests on the pleural fluid should be obtained: description of the fluid, glucose level, differential cell count, microbiologic studies, and cytology ***(Light, 2002)***.

Chapter (II)
Tuberculous Pleural Effusion

Tuberculosis (TB) is a leading cause worldwide of preventable morbidity and mortality from an infectious agent. The interaction of HIV with Mycobacterium Tuberculosis has lead to its resurgence in developed nations and has increased the burden of TB cases in developing countries ***(Who, 2006)***.

TB pleural effusion, considered as a form of extrapulmonary TB (EPTB), constitutes a frequent clinical problem ***(Sharma, 2004)***.

It's particularly important in the present era of HIV infection, when EPTB is more commonly encountered in clinical practice ***(Harries, 1990)***.

A pleural effusion occurs in approximately 5% of patients with TB ***(Siebert et al., 1991)***.

Epidemiology:

A total of nine million new cases and approximately two million deaths from TB were reported in 2004 ***(Who, 2006)***.

Although the African region has the highest estimated incidence (356 per 100,000 population per year), the majority of patients with TB live in the most populous countries of the Asian subcontinent, which accounts for nearly half of the new cases that arise yearly ***(Dye, 2006)***.