C-reactive Protein Measurement for the Differentiation Between Tuberculous and Malignant Pleural Effusion

Thesis submitted for partial fulfillment of the master degree in Chest Diseases

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﴿بسم الله الرحمن الرحيم﴾

قَالوا سُبْحَانَكَ
لا عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ
أَنتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

البقرة آية ٣٢

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The candidate

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LIST OF Abbreviations

ADA	Adenosine deaminase
AFB	Acid Fast bacilli
AFP	Alpha - Fetoprotein
AIDS	Acquired immunodeficiency syndrome
ANA	Anti-nuclear antibody
ARDS	Adult respiratory distress syndrome
AS	Ankylosing spondylitis
CAP	Community acquired pneumonia
CBC	Complete Blood Count
CD	Cluster of differentiation
CEA	Carcino embryonic antigen
CO2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
Cx	Complement
CXR	Chest X-ray
CYFRA 21-1	Cytokeratin -19 fragments
DNA	Deoxyribo nucleic acid
ESR	Erythrocyte sedimentation rate
Fn	Fibronectin
FVC	Forced Vital Capacity
GIST	Gastro intestinal stromal tumor
H	Hydrogen
HAP	Hospital acquired pneumonia
HCC	Hepato cellular carcinoma
HS	Highly significant
Ig	Immunoglobulin
ILx	Interleukin
INF-y	Gamma interferon
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LE	Lupus erythromatosus

MAF	Migration activating factor
MPE	Malignant pleural effusion
MIF	Migration inhibitory factor
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NK	Natural killer cell
NO.	Number
NS	Non-significant
PAF	Platelet activating factor
PC	Phosphokinase
PO2	Partial pressure of oxygen
PGE	Prostaglandin E
PID	Pelvic inflammatory disease
PMNL	Polymorph nuclear leucocytes
PPD	Purified protein derivative
RA	Rheumatoid arthritis
RAM	Rapid agglutination method
SAA	Serum amyloid A
SD	Standard deviation
SLE	Systemic lupus erythromatosus
TBP	Tuberculous pleuritis
TGF-B	Transforming growth factor B
TLC	Total lung capacity
TNF	Tumour necrosing factor
U/S	Ultrasound
UTI	Urinary tract infection
VATS	Video assisted thoracic surgery
VHS	Very highly significant

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Introduction

Pleural effusion is defined as an accumulation of fluid in the pleural space in excess of 15-20 ml. The etiology for the development of a pleural effusion includes changes in the hydrostatic or colloid-osmotic pressure of pleural and pulmonary capillaries, changes in pleural vascular permeability and impaired lymphatic drainage **(Ahmad et al., 2009).**

The most frequent causes of pleural effusion are tuberculosis and neoplasm **(Light, 1995)**. The diagnosis of effusion, need extensive procedure **(Kinasewitz, 1997).** These procedures include cytological, bacteriological, chemical analysis. **Peek et al. (2000)** advocated computerized axial tomography or chest U/S can reveal underlying lung disease or localized effusion.

Pleural needle biopsy, bronchoscopy, thoracoscopy or even open lung biopsy could evaluate undiagnosed pleural effusion after initial thoracocentesis **(White et al., 2000)**. Infection caused by mycobacterium tuberculosis produces a range of immunological reactions so it would be expected that tuberculous pleural fluid contain a variety of immunologically important cytokines because of

accumulation of immunocompetent cells in the pleural cavity **(Ferrer, 1997)**. Pleural effusion is a common complication of malignant diseases occurs in 50% to 70% of malignancies **(Narseen et al., 2000).**

Carcinoma of the lung is the most common malignancy to invade the pleura (30%) and produces malignant effusions **(Hsu, 1987)**. Carcinoma of breast is second in incidence (25%) **(Iqbbal et al., 2000)**.

Lymphoma account for approximately 20% of all malignant effusions **(Sahn, 1998)**. A less common cause of malignant pleural effusion is the primary tumor of the pleura; malignant mesothelioma **(Hubbard, 1997).**

CRP is an acute phase protein predominantly produced and secreted by hepatocytes. Other cells including lymphocytes, kupffer's cells, monocytes and macrophage can also produce CRP **(Castell et al., 1990).**

The induction of CRP synthesis is triggered by a number of cytokines, chiefly IL - 6, which is released from a variety of cell types but mainly from macrophages and monocytes at inflammatory sites **(Gabay and Kushner, 1999).**

CRP level have been shown to increase in a number of pulmonary disease, notably bacterial infection, inflammation, neoplasia, pulmonary thromboembolism, and some pleural effusion related to other conditions **(Mith and Lipwarth ,1995).**

Although several studies have investigated the levels of CRP in various diseases states, few have focused on its role in patient with pleural effusion. The study has demonstrated that pleural fluid CRP level in tuberculous pleuritis is statistically significantly higher than malignant pleural effusion **(Yilmaz et al., 2000)**.

The mechanism underlying the higher CRP in tuberculous pleuritis patient is not clear. They may be two possibilities. First, a local production of CRP in the pleural cavity of TBP patients enhanced by inducer cytokines especially IL - 6. Alternatively, it may result from leakage of plasma CRP via inflamed pleura because a correlation between serum and pleural fluid CRP levels was demonstrated **(Yew et al., 2002).**

Aim of the work

The aim of this study is to determine the validity of pleural fluid C-reactive protein concentration for the differentiation between tuberculous pleuritis (TBP) and malignant pleural effusion (MPE) in patient presenting with lymphocytic exudative 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 cover 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. The visceral and the parietal pleura meet at the lung root. At the pulmonary hilus, the mediastinal pleura is swept laterally onto the root of the lung. Posterior to the lung root, the pleura is carried downward as a thin double fold called the pulmonary ligament **(Light, 2007).**

The function of the pleura, like that of pericardium and peritoneum, is to provide two frictionless surfaces between a mobile structure and the containing walls of its cavity; a thin film of tissue fluid lubricates the surfaces. The cuff of pleura projected around the lung root is too big for it, as a coat cuff is too big for the wrist. It hangs down below as an empty fold, the pulmonary ligament, and an ill-

chosen name for it has nothing to do with the lung and is not a ligament. It provides dead space into which the lung root descends with descent of the diaphragm. More important, allows for expansion of vessels in the lung root, especially the inferior pulmonary vein, which always has 'dead space' near them (e.g. to the right superior vena cava, and in the femoral canal alongside the femoral vein) **(Wang, 1985).**

A film of fluid (pleural fluid) is normally present between the parietal and the visceral pleura. This thin layer of fluid act as 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. It is a potential space rather than an actual one **(Wang, 1998).**

The pleura is lined by a single layer of mesothlial cells. These cells are 20-40 um wide from 0.1 to 0.4 um, and have microvilli on their surface. The microvilli are distributed over the entire pleura, but are most prominent on the caudal as compared to the cephalic portions, and on the visceral as compared to the parietal pleura **(Wang, 1985).**

The microvilli increase the surface area of the pleura and thus enhance membrane transport and other membrane-dependent metabolic functions **(Light, 1983).**

Imuunohistochemically, the mesothelial cells express both low- and high- molecular-weight cytokeratin. The normal mesothelial cells are negative for reaction to vitamin, epithelial membrane antigen, carcinoembryonic antigen and factor VIII-related antigen **(Dervan et al., 1986)** and **(Bolten et al., 1986).**

The mesothelial cells in both visceral and parietal pleurae vary in thickness from less than 1μm to more than 4μm and from 16.4±6.8 to 41.9±9.5μm in diameter. Their shape may vary according to their location in the pleural membrane **(Wang, 1985).**

Blood Supply of the Pleura:

The parietal pleura receives its blood supply from the systemic capillaries. Small branches of the intercostal arteries supply the costal pleura, whereas the mediastinal pleura is supplied principally by the pericardiacophrenic artery. The diaphragmatic pleura is supplied by the superior phrenic and musculophrenic arteries. The venous drainage of the parietal pleura is primarily by the intercostal veins,