



The Egyptian Society of Chest Diseases and Tuberculosis  
**Egyptian Journal of Chest Diseases and Tuberculosis**

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ORIGINAL ARTICLE

# Role of interleukin-6 (IL-6) in diagnosis of malignant pleural mesothelioma



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Received 21 June 2014; accepted 6 November 2014

Available online 2 May 2015

## KEYWORDS

Interleukin-6 (IL-6);  
Mesothelioma;  
Pleural effusion

**Abstract** *Aim of the work:* To evaluate the role of interleukin-6 (IL-6) in diagnosis of malignant pleural mesothelioma by detecting its level in the pleural fluid and serum of the patient with malignant pleural mesothelioma in comparison with other causes of pleural effusion.

*Materials and methods:* This study was conducted on 44 patients (25 males and 19 females) with pleural effusions of different etiologies, at Banha University Hospital from April 2011 to December 2012. These patients were classified according to their final diagnosis into four groups: Group I: included 20 cases with malignant pleural effusions secondary to malignant pleural mesothelioma. Group II: included 7 cases with malignant pleural effusions secondary to metastatic adenocarcinoma. Group III: included 7 cases with tuberculous pleural effusions. Group IV: included 10 cases with transudative pleural effusions. IL-6 measured in both plasma and pleural fluid of selected patients and statistically analyzed.

*Results:* The mean values of pleural fluid IL-6 were higher among patients with malignant effusion (groups I, II), respectively than those with non malignant (groups III, IV), these differences were statistically significant ( $p < 0.001$ ). There was significant increase in pleural fluid IL-6 levels in group (I) mesothelioma mean was ( $1627.4 \pm 294.3$ ) versus group (II) adenocarcinoma mean was ( $1501.1 \pm 274.2$ )  $p < 0.05$  being higher in group (I). There was no significant difference in the mean levels of serum IL-6 in malignant groups (I, II), versus benign groups (III, IV) but there was a high significant increase in pleural fluid IL-6 level in malignant groups (I, II) mean was ( $1590.7 \pm 294.6$ ) versus benign groups (III, IV) mean value was ( $1260.6 \pm 145.5$ ).  $p < 0.001$  being higher in malignant groups.

*Conclusion:* Pleural fluid level of interleukin-6 can be used as diagnostic tool for malignant pleural mesothelioma (MPM). Pleural fluid level of interleukin-6 (IL-6) can be used in differentiating malignant from non malignant effusions, pleural effusions secondary to malignant pleural mesothelioma (MPM) from those secondary to Adenocarcinoma.

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Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.

<http://dx.doi.org/10.1016/j.ejcdt.2014.11.005>

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## Introduction

Pleural effusions are often a diagnostic dilemma as the differential diagnosis is wide [1]. However, in about 5–10% of cases the effusions remain undiagnosed after the initial evaluation and 20% of these effusion are later proved to be malignant [2]. Cytokines are proteins with relatively low molecular weight that are secreted by cells in response to a variety of different stimuli and act as key mediators of the host response to various infections, inflammatory and immunologic challenges [3]. IL-6 is a pleiotropic cytokine stimulating a variety of cell types [4]. Mesothelioma cells and cell lines have been reported to produce IL-6 [5]. Since IL-6 is relatively stable and its concentrations can be measured in synovial or cerebrospinal fluid the measurement of IL-6 in the body fluid would be useful to determine the activity of inflammation in patient with complicated conditions [6,7]. IL 6 role as an anti-inflammatory cytokine is mediated through its inhibitory effects on TNF-alpha and IL-1, and activation of IL 10 [8]. IL 6 plays a central role in host defense against infection and tissue. IL 6 elicits cellular actions by binding to the membrane bundle IL 6 receptor [7].

Because IL 6 is an autocrine growth factor for many cell types, its hyperproduction has been associated with a variety of malignancies including plasmacytoma, multiple myeloma, uterine cervical carcinoma and Kaposi's sarcoma [9,10].

## Patients and methods

This study was conducted on 44 patients with pleural effusions of different etiologies, at Banha University Hospital from April 2011 to December 2013 after approval of the study protocol by the Local Ethical Committee and obtaining written fully informed patients' consent. These patients were classified according to their final diagnosis into four groups: Group I: malignant pleural effusions secondary to malignant pleural mesothelioma. Group II: malignant pleural effusions secondary to metastatic adenocarcinoma. Group III: tuberculous pleural effusions. Group IV: transudative pleural effusions.

### Exclusion criteria

1. Any effusion due to undetermined cause or suspected to have more than one possible cause.
2. Minimal effusions.
3. Patients already started any kind of treatment.

All patients were subjected to the following: (1) Full medical history and clinical examination, routine laboratory investigations, radiological examination (CXR & CT chest), abdominal ultrasonography, echocardiography whenever needed. (2) Tuberculin skin test and Sputum examination for acid fast bacilli (AFB) by Ziehl-Neelsen stain. 3-Fiber-optic bronchoscopy: for patients with suspected bronchogenic carcinoma where tissue biopsies or bronchoalveolar lavage (BAL) was sent for histopathological examination. Diagnostic thoracentesis: was done to all patients for physical, chemical, bacteriological examination and cytological examination. Quantitative measurement of pleural fluid IL-6 and using ELISA technique. Pleural biopsies: were taken for all patients in groups (I, II, and III). Venous blood samples for quantitative estimation of serum IL-6. Quantitative measurement of

IL-6 in serum and pleural fluid using ELISA kit supplied by KOMA BIOTECH INC. Catalog No. K03394.

### Statistical analysis

The collected data were analyzed using SPSS version 16 software. Chi square test ( $\chi^2$ ), student "t" test and ANOVA were used as tests of significance. ROC curve was used to detect cut-off values of IL-6 with optimum sensitivity and specificity. Stepwise multiple regression analysis was done to detect the significant predictors of IL-6.

## Results

The mean of age (in years) of group I was  $65.9 \pm 12.4$ , group II was  $65 \pm 9.8$ , group III was  $53.1 \pm 6.94$  and group IV was  $62 \pm 8.5$  years with male predominance 56.8%. The most common presenting complaints were shortness of breath ( $n = 42$  cases, 95.5%) followed by cough that occurred in ( $n = 41$  cases, 93%), then chest pain ( $n = 38$  cases, 86.4%), fever ( $n = 12$  cases, 27.3%) and hemoptysis ( $n = 6$  cases, 13.6%). The classic radiographic picture was homogenous opacity with concave upper border rising toward the lateral chest wall it may be moderate sized effusions ( $n = 19$  cases, 44.2%), while cases with massive effusion showed complete or near complete opacification ( $n = 15$  cases, 34.9%), and mild effusion ( $n = 9$  cases, 20.9%). Right side effusions were 27 cases, 62.8%, left-sided 11 cases 25.6% and bilateral 5 cases 11.6%. Tuberculin skin test was positive in 3 cases in group (I) mesothelioma representing 15%, and 7 cases in group (III) TB representing 100% and lastly all cases were negative in group (II adenocarcinoma, IV control). The mean levels of platelets was higher in mesothelioma (I) followed by TB effusion (III) and lastly adenocarcinoma (II) versus group (IV) and these was significance difference as  $p < 0.001$ .

The mean values of serum and pleural fluid protein levels were as the following: group (I) ( $4.47 \pm 0.77$  and  $3.9 \pm 0.82$  g/dl), respectively, in group (II) ( $4.35 \pm 0.76$  and  $4.7 \pm 1.01$  g/dl), respectively, in group (III) ( $3.94 \pm 0.60$  and  $4.2 \pm 0.50$  g/dl) the ratios of PLF/SPTn were always more than 0.5 in the three exudative groups. While in group (IV) ( $4.8 \pm 0.89$  and  $2.3 \pm 0.48$  g/dl), respectively, and the ratios of PLF/SPTn were always less than 0.5.

The mean values of serum and pleural fluid LDH levels were as following: group (I) ( $109.9 \pm 16.7$  and  $1107.6 \pm 296.8$  U/L), respectively, in group (II) ( $117.0 \pm 12.9$  and  $927.5 \pm 388.2$  U/L). In group (III) ( $102.0 \pm 11.8$  and  $805.8 \pm 330.8$  U/L), respectively. and the ratios of FLDH/SLDH were more than 0.6 and the absolute values of FLDH were more than 200 IU/L and more than 2/3 of the upper limit of the serum in the three exudative groups. While in group (IV) control, the mean levels was ( $276.6 \pm 35.9$  and  $194.2 \pm 29.7$  IU/L), respectively, and the ratio of FLDH/SLDH was less than 0.6 and the absolute values of FLDH were less than 200 IU/L and less than 2/3 of the upper limit of normal serum.

As regard glucose level in serum and pleural fluid the lowest mean level of pleural fluid glucose was found in tuberculous pleural effusion ( $52.5 \pm 20.5$ ) followed by pleural effusion secondary to mesothelioma ( $54.7 \pm 28.9$ ) then pleural effusion secondary to adenocarcinoma ( $68.3 \pm 17.2$ ) and lastly transudative effusion ( $72 \pm 22.8$ ).

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