Egyptian Journal of Chest Diseases and Tuberculosis (2016) **65**, 605–612

HOSTED BY

The Egyptian Society of Chest Diseases and Tuberculosis

Egyptian Journal of Chest Diseases and Tuberculosis

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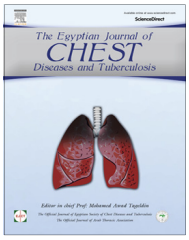

ORIGINAL ARTICLE

The role of tumor necrosis factor alpha in differentiation between malignant and non malignant pleural effusion

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Received 13 August 2015; accepted 8 February 2016
Available online 8 April 2016

KEYWORDS

Pleural effusion;
Malignant;
Non malignant;
TNFα

Abstract *Background:* Despite the fact that Light's criteria remain the gold standard approach in differentiating exudates from transudates, several fluid markers have been introduced for establishing the cause of pleural effusion to differentiate types of pleural exudate.

Aim: The aim of this study was to explore means of discriminating between malignant and non malignant pleural effusions.

Methods: The study conducted on 45 patients (28-males and 17 females) with pleural effusions of different etiologies. They were classified according to their final diagnosis into four groups: Group I: 10 cases (6 males and 4 females) with tuberculous pleural effusions. Group II: 15 cases (8 males and 7 females) with malignant pleural effusions. Group III: 10 cases (7 males and 3 females) with parapneumonic effusion. Group IV: 10 cases (7 males and 3 females) with transudative pleural effusions included as a control group. The complete biochemical analysis of pleural fluid, pleural fluid culture, and pathological examination of pleural fluid and tissue was performed. Moreover, quantitative measurement of TNF-α in serum and pleural fluid using ELISA was performed.

Results: Levels of TNF-α were significantly higher in the pleural fluid of exudative nature compared to transudative type. There was a significant increase in pleural fluid TNF-α level in non malignant effusions (tuberculous and parapneumonic) compared with malignant effusion. Also there was a significant increase in pleural fluid TNF-α level in tuberculous effusion versus malignant effusion. These results indicate that TNF-α may be considered a sensitive marker in differentiation between malignant and non malignant pleural effusions.

Conclusion: Pleural fluid level of TNF-α can be used in differentiating malignant from non malignant effusion. Also levels of TNF-α in the serum and pleural fluid could be useful as a complementary marker in the differential diagnosis of two most common types of exudates (tuberculous and malignant).

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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.2016.02.008

Introduction

A pleural effusion refers to an abnormal accumulation of fluid in the pleural cavity, it is often a result of local pleuropulmonary diseases but can also complicate many systemic pathologies. Pleural effusion develops when the rate of pleural fluid formation exceeds that of its drainage. Establishing the underlying cause of pleural effusion is often challenging because a wide range of local and systemic diseases can lead to pleural effusion formation. Pleural fluid samples should be analyzed to determine whether it is a transudate or exudate [10].

This distinction determines not only the differential diagnosis and thus the following therapeutic intervention, but also the underlying pathophysiologic mechanisms which lead to the aggregation of fluid in the pleural cavity. Indeed, an exudative pleural effusion occurs when the permeability of the mesothelial capillary barrier to albumin and other macromolecules is elevated. In contrast, the presence of a transudate indicates that the systemic or pulmonary pressures influencing the formation or reabsorption of pleural fluid are altered [6].

Despite the fact that Light's criteria remain the gold standard approach in differentiating exudates from transudates, several fluid markers have been introduced for diagnostic analysis. The measurement of pleural fluid interleukin-6, TNFα, CRP, interferon-gamma, interleukin-1 and immunological cytokines has been shown to be beneficial to the diagnosis of exudative pleural effusion [17].

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. Cytokines are thought to exert their effects by binding to specific receptors on the surface of the cell, although cytokines may in some instances have direct membrane effects [14].

Tumor necrosis factor alpha (TNF-α), isolated 30 years ago, is a multifunctional cytokine playing a key role in apoptosis and cell survival as well as in inflammation and immunity. Although named for its antitumor properties, TNF-α has been implicated in a wide spectrum of other diseases [23].

Tumor necrosis factor-α is a small polypeptide with pleiotropic effects on biological and immunological processes. It is a key cytokine in inflammatory reactions, and high levels of this cytokine in pleural fluid have been detected in several diseases that cause pleural effusion [13].

Patients and methods

This study was conducted on 45 patients (28-males and 17 females) with pleural effusions of different etiologies, at Benha University Hospital and Elmehlla chest hospital during the period from December 2012 till December 2013 after approval of the study protocol by the Local Ethics Committee and obtaining fully written informed patients' consent. The patients were classified according to their final diagnosis into four groups: Group I: 10 cases (6 males and 4 females) with tuberculous pleural effusions. Group II: 15 cases (8 males and 7 females) with malignant pleural effusions. Group III: 10 cases (7 males and 3 females) with para-pneumonic effusion. Group IV: 10 cases (7 males and 3 females) with transudative pleural effusions of congestive heart failure included as a control group (Table 2).

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 subjects were submitted to the following

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 thoracocentesis: was done to all patients for physical, chemical, bacteriological examination and cytological examination. Quantitative measurement of pleural fluid TNFα using ELISA technique. Pleural biopsies were taken for all patients in Groups (I, II, and III) according to the case. Venous blood samples for quantitative estimation of serum TNFα. Quantitative measurement of TNFα in serum and pleural fluid using ELISA kit supplied by BOSTER Biological Technology Catalog No. EK0525.

Statistical analysis

Data collected were analyzed using SPSS version 20 software. Chi square test (v2), Student's "*t*" test and ANOVA were used as tests of significance. ROC curve was used to detect cutoff values of TNFα with optimum sensitivity and specificity. Stepwise multiple regression analysis was done to detect the significant predictors of TNFα.

Results

The mean age (in years) of Group I was 50.3 + 15.1, Group II was 67.6 + 10.4, Group III was 46.1 + 11.9 and Group IV was 59.1 + 10.7 years with male predominance (Table 1).

The mean values of pleural fluid and serum TNF-α levels were as follows: Group (I) (258.3 + 70.6 and 35.5 + 7.43 pg/ml), respectively, in Group (II) (50.8 + 18.1 and 26.8 + 6.31 pg/ml). In Group (III) (88.1 + 35.4 and 26.9 + 10.1 pg/ml), respectively. While in Group (IV) control, the mean levels were (21.4 + 8.9 and 18.8 + 7.15 pg/ml), respectively, (Table 4). There was a statistically significant difference in the serum and the pleural fluid mean values of TNF-α among the four groups ($P = 0.001$) with a statistically significant difference between tuberculous Group (I) which showed the statistically significant highest mean and the three other groups in which transudative group showed the statistically significant lowest mean (Table 3 and Figs. 1–3).

There was a significant difference in the mean levels of serum and PL TNF-α in exudative effusions (mean was 29.1