Journal of Infection (2005) **50**, 114–119

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Correlation between levels of tumour necrosis factor-α and levels of pH, glucose, and lactate dehydrogenase in parapneumonic effusions

M. Odeh[a,*], E. Sabo[b], I. Srugo[c], A. Oliven[a]

[a]*Department of Internal Medicine B, Bnai Zion Medical Center, Technion Faculty of Medicine, Israel Institute of Technology, P.O. Box 6477, Haifa 31063, Israel*
[b]*Department of Pathology, Carmel Medical Center, Technion Faculty of Medicine, Israel Institute of Technology, Haifa, Israel*
[c]*Department of Microbiology, Bnai Zion Medical Center, Technion Faculty of Medicine, Israel Institute of Technology, Haifa, Israel*

Accepted 19 May 2004

Available online 1 July 2004

KEYWORDS
Parapneumonic effusion;
TNF-α; pH; Glucose;
Lactate dehydrogenase

Summary *Objectives.* This study was undertaken to investigate the correlation, which has not been previously investigated, between levels of tumour necrosis factor-α (TNF) and levels of pH, glucose, and lactate dehydrogenase (LDH) in pleural fluid of patients with uncomplicated parapneumonic effusion (UCPPE), and patients with complicated parapneumonic effusion (CPPE).

Methods. Using a commercially-available high sensitivity ELISA kit, levels of TNF were measured in pleural fluid of patients with UCPPE ($n = 23$), and CPPE ($n = 15$), and were compared with levels of pH, glucose, and LDH in these two groups.

Results. The mean ± SD values of pleural fluid TNF, pH, glucose, and LDH in the UCPPE group were 11.05 ± 7.65 pg/ml, 7.41 ± 0.08, 125 ± 48 mg/dl, and 306 ± 182 IU/l, respectively. In the CPPE group the values were 56.07 ± 28.5 pg/ml, 6.82 ± 0.25, 42 ± 36 mg/dl, and 2096 ± 1916 IU/l, respectively. The only significant correlation, which was negative, was found between levels of TNF and pH in the CPPE group ($r = -0.62$, $P = 0.01$). Levels of pleural fluid TNF and LDH were significantly higher, and levels of glucose were significantly lower in the CPPE group than in the UCPPE group ($P < 0.0001$).

Conclusions. This study demonstrates, for the first time that TNF levels correlate inversely with levels of pH in pleural fluid of patients with CPPE but not of patients with UCPPE. This correlation may, in part, explain the pathophysiology of the pleural complications which occur in the presence of CPPE.

Introduction

Parapneumonic effusions (PPEs) are the most common exudative pleural effusions; approx. 40% of patients with bacterial pneumonia have an accompanying pleural effusion.[1] These effusions may either

*Corresponding author. Tel.: +972-4-8359775; fax: +972-4-8371393.
E-mail address: majed.odeh@b-zion.org.il

0163-4453/$30.00
doi:10.1016/j.jinf.2004.05.016

resolve with antibiotic therapy alone, or follow a complicated course requiring tube thoracostomy.

Based on the characteristics of a diagnostic thoracentesis, PPE can be classified into uncomplicated PPE (UCPPE), complicated PPE (CPPE), or empyema.[2] UCPPEs are not infected, have a pH level >7.20, a glucose level greater than 60 mg/dl, and a lactate dehydrogenase (LDH) level less than 1000 IU/l. CPPEs usually are infected, have a pH level less than 7.20, a glucose level less than 60 mg/dl, and an LDH level greater than 1000 IU/l. CPPEs are initially thin and serous, but become more purulent as disease progresses. A complicated effusion is called an empyema when the effusion becomes thick and turbid (pus).[2-5] UCPPEs can be managed by systemic antibiotics, and usually do not need tube thoracostomy. CPPEs, besides systemic antibiotic treatment, usually require tube thoracostomy and/or other surgical treatments.[2-5]

Because the diagnostic sensitivities of pleural fluid cultures and Gram stain are low, determination of pleural fluid pH, glucose and LDH are recommended for discrimination between UCPPE and CPPE.[6,7] However, no general consensus exists regarding the clinical usefulness of these criteria.[6,7] Measurement of pH was found to be superior to glucose and LDH measurements in predicting CPPEs in a previous meta-analysis study.[7]

Tumour necrosis factor-α (TNF) 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, including UCPPE and CPPE.[8-11] We[12,13] and others[14] have recently shown that pleural fluid TNF concentrations are significantly higher in CPPE than in UCPPE. Furthermore, we also have shown that levels of TNF correlate positively with polymorphonuclear leucocyte counts in pleural fluid of patients with PPE, complicated or uncomplicated.[13]

To date, there are no data regarding correlation between levels of TNF in pleural effusion and those of biochemical markers for discrimination between UCPPE and CPPE. The aim of this study is to investigate the correlation between levels of TNF and levels of pH, glucose, and LDH in pleural fluid of patients with UCPPE and CPPE.

Patients and methods

Patients

The study population consisted of 38 consecutive in-patients with PPE, 23 patients (13 males; 10 females) aged 29–91 years were with UCPPE, and 15 patients (nine males; six females) aged 32–92 years were with CPPE. Effusion were considered UCPPE when there was an acute febrile illness with purulent sputum, pulmonary infiltrate and responsiveness to antibiotic treatment, in the absence of other diseases causing pleural effusion, and with no evidence of bacterial invasion of the effusion by Gram stain and cultures, absence of loculations in the pleural cavity, and pleural fluid pH ≥ 7.20. In all patients with UCPPE the pleural effusion completely resolved by antibiotic treatment only. CPPE was considered in the presence of pneumonia confirmed clinically and radiographically in the absence of other diseases causing pleural effusion, with at least one of the following indicators of bacterial invasion of the effusion: bacteria in the Gram stains or culture, presence of loculations in the pleural cavity, and pH <7.20. All patients with CPPE needed medical and surgical treatment.

Techniques

Pleural fluid samples were obtained by intercostal needle aspiration. Thoracentesis was performed as a routine diagnostic and therapeutic procedure but not particularly for our study. All pleural fluids were tested for pH, glucose, LDH, total protein, and leucocyte and differential count. The fluids were also analysed cytologically for the presence of tumour cells, and cultured and stained for the presence of bacteria. All the patients with UCPPE were treated only with antibiotics, and those with CPPE were treated with antibiotics and invasive surgical procedures. The study was approved by the ethical committee of our medical center.

Measurement of TNF concentration

Samples of pleural fluid were immediately centrifuged at 2500 rpm, at 4 °C centrifuge temperature for 10 min. The supernatants were stored at -70 °C until assay which was performed within 4 months of sample storage. TNF concentrations were measured using commercially available (Quantikine HS, R&D Systems, Minneapolis, MN, USA) solid-phase, high sensitivity enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's recommendations. This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for TNF has been precoated onto a microplate. Standards and samples were pipetted into the wells, and any TNF present was bound by the immobilized antibody. After washing away any unbound substances, an