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ORIGINAL ARTICLE

Evaluation of pleural fluid YKL-40 as a marker of malignant pleural effusion☆

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Abstract The glycoprotein YKL-40 is synthesized both by cancer cells and by tumor-associated macrophages and plays a functional role in tumor progression. Consequently, high serum YKL-40 levels have been associated with a poor prognosis in patients with several cancer types.

The aim of this study is to assess pleural effusion and serum concentrations of YKL-40 in patients with different types of pleural effusions and to evaluate the diagnostic performance of YKL-40 in detecting malignant pleural effusion.

Patients and methods: A prospective cohort study was carried out of 88 consecutive patients presenting with pleural effusions. The patients were divided into four groups: 22 patients with transudative effusions, 24 patients with parapneumonic pleural effusion and 8 patients with tuberculous pleural effusion and 34 patients with malignant pleural effusions. Blood and pleural fluid YKL-40 levels were measured using enzyme-linked immunosorbent assay.

Results: Both serum HE4 levels and pleural effusion YKL-40 levels were significantly higher in patients with malignant effusions than in patients with transudative or non-malignant exudative effusions. A pleural fluid YKL-40 cut-off value of 256 ng/mL was found to predict malignant pleural effusions with a diagnostic sensitivity of 85.3% and specificity of 90.7%.

Conclusion: The current study reports a finding of increased serum and pleural fluid YKL-40 levels in patients with malignant pleural effusions compared to non-malignant effusions.

Introduction

Pleural effusion is a commonly encountered presentation in clinical practice, with a large number of possible causes, including disease localized to the lung, primary or metastatic pleural disease or a manifestation of systemic disease. The differential diagnosis of a pleural effusion is wide, and pleural

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fluid analysis is usually the first step toward identifying the cause of a pleural effusion. It gives an indication about the underlying pathophysiologic process and the need for further investigations [1]. Light's criteria is the most commonly used parameter for the differentiation between exudative and transudative effusions [2] as it is a very robust test with a diagnostic accuracy of 93–96% [3]. Malignant pleural effusions are a frequent cause of exudative effusions, and their diagnosis often poses a clinical challenge as pleural fluid cytology is only positive in around 60% of cases on average [4,5]. More invasive procedures such as thoracoscopy or thoracotomy may be required to reach a diagnosis, but at the expense of higher morbidity [6]. Numerous studies have been published analyzing the potential utility of different tumor markers in pleural effusions [7,8]. The chitinase-like protein YLK-40, also known as human cartilage glycoprotein 39, is a glycoprotein produced in association with various inflammatory and malignant processes [9,10]. It is mainly secreted by macrophages, synovial cells, chondrocytes, and neutrophils [11,10]. Although the exact physiological function of YKL-40 protein is unknown, the pattern of its expression suggests a role in inflammation and tissue remodeling. Elevated serum YKL-40 levels have been found in a wide range of inflammatory diseases including asthma, cirrhosis, sarcoidosis, osteoarthritis, cardiovascular disease, diabetes mellitus, rheumatoid arthritis, chronic obstructive pulmonary disease, and inflammatory bowel disease. High serum concentration of YKL-40 has also been found in various malignancies and seems to be a marker for decreased survival [12–14]. YKL-40 is not specific for SCLC. It is secreted by many different types of solid carcinomas and also by non-malignant cells in tissues characterized by inflammation, tissue degradation/remodeling or ongoing fibrogenesis. YKL-40 is produced by macrophages, neutrophils, malignant tumor cells, mesothelial cells and arthritic chondrocytes [15], and has been found in the fibrotic liver [16]. Elevated serum YKL-40 levels are found in patients with non-malignant diseases such as severe active rheumatoid arthritis, severe bacterial infections and liver fibrosis [17]. YKL-40 has been shown to be associated with lung injury pathogenesis contributing to inflammation, remodeling and cellular proliferation [18].

The aim of the current study was to assess pleural effusion and serum concentrations of YKL-40 in patients with pleural effusions of varying characteristics, and to evaluate the diagnostic performance of YKL-40 in detecting malignant pleural effusions.

Patients and methods

A prospective cohort study was carried out of 88 consecutive patients with pleural effusions seen in the pulmonary and Oncology Departments of King Fahad Hospital Dammam. The patients were subsequently divided into four groups according to the type of effusion: transudative effusion (TPE), parapneumonic pleural effusion (PPPE), tuberculous pleural effusion (TBPE), and malignant pleural effusion (MPE). Light's criteria were calculated to differentiate exudative from transudative effusions. An effusion was classified as malignant if tumor cells were found in the pleural fluid or pleural biopsy, or in a patient with disseminated malignancy and no alternative explanation for an exudative effusion. Parapneumonic effusion was defined as; the presence of pleural effusion in patients with community-acquired pneumonia. We used The American Thoracic Society criteria for defining the pneumonia [newly occurred respiratory symptoms, fever and abnormal breath sounds, together with a new pulmonary infiltration on chest X-ray, and consistent laboratory findings (leukocytosis count and high serum CRP levels) and neutrophilic pleural effusion] [19]. Pleural fluid samples were diagnosed as tuberculous effusion by pleural biopsy specimen showing granulomas with caseification necrosis, or pleural fluid positive on Ziehl-Nielsen stain or Lowenstein-Jensen culture, or pleural fluid consistent with clinical signs and symptoms of tuberculosis together with lymphocyte predominance in pleural effusion and good response to anti-tuberculosis treatment. The study thereafter comprised twenty-two patients with transudative effusions, twenty-four patients with parapneumonic effusions, eight patients with tuberculous effusion and thirty-four patients with malignant effusions. Patients with transudative effusions comprised 12 women and 10 men and were aged (Mean ± SD) 60.2 ± 6.5 years. Patients with parapneumonic effusions comprised 13 women and 11 men and were aged (Mean ± SD) 59.8 ± 5.4 years. Patients with tuberculous effusions comprised 3 women and 5 men and were aged (Mean ± SD) 58.9 ± 8.9 years. Patients with malignant effusions comprised of 18 males and 16 females and were aged; (Mean ± SD) 63.5 ± 8.3 years (Table 1). Twenty-three patients had lung cancer, 2 metastatic colon adenocarcinoma, 2 patients with non Hodgkin lymphoma, 2 patients with metastatic gastric cancer and 5 patients with metastatic breast cancer. Of the 23 patients with bronchial carcinoma, histopathologically the cases comprised of 11 adenocarcinoma (3 of them were well differentiated and 8 were moderately differentiated), 12 cases of squamous cell carcinoma (3 of them were moderately differentiated and the other 9 poorly differentiated). Five out of the 11 distant metastatic cases originated from breast cancer, and they were microscopically invasive ductal carcinoma not otherwise specified (NOS), ranging from grade II/III to grade III/IV. All patients included in this study had unilateral pleural effusion except 2 patients of the transudative group with congestive heart failure. As per institution guidelines, the study was approved by King Fahad Hospital Ethics Committee. Informed consent was obtained from each patient included in the study. Thoracocentesis was performed under the aseptic technique, and pleural effusion and serum samples were collected at the same time. The pleural fluid was collected in tubes containing EDTA for determination of the cellular content, in plain tubes for determination of LDH, protein, albumin and YKL-40 levels. Paired serum samples were analyzed for urea, creatinine, albumin, total protein, and LDH levels. These parameters were measured using Siemens Diagnostics (Marburg GmbH, Germany) (RxL Dimension Clinical Chemistry analyzer) [20]. Pleural fluid pH was measured using blood gas analyzer, GEM premier 3000 (instrumentation laboratory, USA). Sample for pleural fluid pH was collected anaerobically, kept on ice and analyzed immediately within five minutes of collection. Pleural adenosine deaminase (ADA) levels were also measured as UI/mL. For serum YKL-40 analysis, the blood samples were centrifuged at 3000*g* for 10 min at 4 °C. After the centrifugation, the serum was removed and transferred into a clean test tube. All pleural and serum samples were stored in a refrigerator at −80 °C until YKL-40 analysis and they were dissolved and stored for 24 h at