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Interleukin-17 concentration as a biomarker in diagnosis of exudative pleural effusion compared with benign pleural effusion

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ABSTRACT

Pleural effusion is one of signs and complications resulting from malignant disease such as lung and breast cancer, and also tuberculosis and infective lung disease by cytological analysis of pleural fluid we can use of tumor marker and other biomarkers to better diagnose malignant pleural effusion.in this study we examined the concentration of interleukin-17 in pleural fluid with causes of exudative pleural effusion in the patients referred to hospital of 2015-2016.This is a descriptive-analytical and case-control study and 130 patients with exudative pleural effusion were enrolled in the study after an informed consent samples collected from the patients divide into two main group including 88 patients with malignant pleural effusion and 42 patient with benign effusion. in the next step by using of the same previous pleural fluid samples, the concentration of interleukin-17 was measured with ELISA by specific kit after entering to computer through SPSS-18 statistical software, description of data was done into frequency and percentage.Interleukin-17 concentration was (69.73±64.58) in patients with malignant causes and (55.32±43.60) in benign causes.The results showed that this different was statistically significant (P=0.02) and interleukin -17 rate, is higher in the malignant pleural effusion.According to higher levels of interleukin-17 in malignant pleural effusion maybe we can achieve important result in differentiating between malignant and non-malignant pleural exudate, without the need for invasive procedures, by putting together the clinical symptoms, the interleukin-17 concentration in pleural fluid and pleural fluid cytology results.

KEY WORDS: INTERLEUKIN-17, EXUDATIVE PLEURAL EFFUSION, MALIGNANT PLEURAL EFFUSION, BENIGN PLEURAL EFFUSION, BIOMARKER

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INTRODUCTION

Pleural effusion is an excessive accumulation of fluid in the pleural space, which affects annually about one million people around the world. There are a range of causes for the disease; benign diseases such as infections, heart and liver failures, rheumatic diseases and drugs on the one hand and fatal cancers of lung and other visceral organs on the other hand are placed in this spectrum (Esther et al 1997).

Plain chest pleurography is a simple diagnostic measure to detect pleural effusion, which appears as flattening and displacement between costophrenic angles. With the presence of less fluid or abnormal localization, ultrasound or CT scan can be used to conduct pleural tap (Heffner et al 1997, Light et al 1972, Ryland et al1998). Cytologic analysis of pleural fluid is the most common method for diagnosis of malignancy; while the specificity of cytologic findings is 100%, unfortunately only about 60% of malignant effusions can be detected through this technique (Alema'n et al 2010). For undiagnosed exudative effusions with suspicion of malignancy but negative cytology, more invasive approaches are necessary (Hooper et al 2010 Chun Hua et al., 2017).

Closed pleural biopsy has less additional diagnostic value and thoracoscopy is the preferred method, since it is diagnostic in 90% of patients (Light 2006, Roberts 2010 and Neragi-Miandoab 2006). However, there is no possibility of access to this invasive procedure in all centers. Many investigations have assessed the ability of tumor markers and other biomarkers to improve the diagnosis of MPE (Botana-Rial et al 2011, Kremer et al 2010).The combined use of different markers has also been proposed in some studies (Kremer et al 2010, 2013).

Unfortunately, none of these markers has shown the sensitivity and specificity enough to select as a diagnostic marker of MPE (Hooper et al 2010). In a study, a type of chemical safety approach has been used to search for non-invasive markers of lung cancer in PE (Porcel et al 2004). In this regard, several chemical biomarkers of inflammation were found that were differentially expressed in MPE vs. BPE. Among these biomarkers, IL-17 and CEA were expressed at higher quantities in MPE than BPE. Interleukin 17 is a potential inflammatory cytokine produced by Th17 cells; it is expected to be used as a marker for the diagnosis of pleural effusion. The aim of this study is to determine the concentration of IL-17 in pleural fluid to facilitate differentiation between MPE and BPE.

MATERIALS AND METHODS

The Deputy of Science and Technology of Golestan University of Medical Sciences and Research Ethics Committee approved study design and implementation protocol. All actions taken, had no physical, psychological or financial losses for the participants in the research. This descriptive and analytical study was performed on 130 patients with exudative pleural effusion who were admitted to Shahid Sayyad Shirazi Teaching Hospital in Gorgan during 2015-2016, and enrolled in the study after obtaining informed consent.Routine diagnostic procedures such as X-ray, CT scan and ultrasound, if necessary, were performed for all patients before starting the study. After history taking and exact physical examination, thoracentesis was carried out to prepare pleural fluid samples that were frozen at -20°C after centrifugation for 15 min.

The samples were analyzed for biochemical properties, pH, glucose and proteins; accordingly, exudative pleural effusion was differentiated from transudative type and patients with transudative pleural effusion were excluded from the study. Malignancy of pleural effusion was diagnosed according to our and previous studies using VATS technique; such that, after inserting VATS instruments through 1 to 2 incisions and after viewing the parietal and visceral pleura as well as evidence of metastases, biopsy was performed from the parietal pleura and pleural fluid for cytology testing. The samples were sent to the pathology laboratory for detecting malignancy and its type.

In terms of etiology and based on the findings of the gold standard of pleural fluid analysis (microbiology and cytology testing, including cell differential count), exudative pleural effusion were classified into two main MPE and BPE groups. According to previous studies, since between 40 and 50 percent of the cases showed malignant exudative pleural effusion, so the samples were divided almost with the same proportion. At a later stage, by using the same previous pleural fluid samples, the IL-17 levels were measured via ELISA kit according to the manufacturer's protocol and the samples were stored at -80°C until testing.Having pleural effusion disease was inclusion criterion. Exclusion criteria included transudative pleural effusion, diabetes, autoimmune diseases and rheumatic diseases.

Data were analyzed using statistical SPSS V.18 software. Normal distribution and data homogeneity were assessed using the Kolmogorov-Smirnov test.

In addition, the mean IL-17 level was compared between the two groups using independent t-test. Mann-Whitney test was applied for normal distribution of IL-17 concentration. Significance level of the tests was 0.05.

RESULTS AND DISCUSSION

After examining, 130 patients were divided into two groups of malignant pleural effusion (n=88, 67.7%) and

benign pleural effusion (n=42, 32.3%) with a mean age of 57 and 59 years respectively. There was no statistically significant difference between IL-17 level and age of the patients. The patients in MPE group included 44 males (50%) and 44 females (50%), but the patients in BPE group consisted of 26 males (61.9%) and 16 females (38.1%).

In the MPE and BPE groups, 41 and 21 people were smokers respectively. Among the patients in MPE group, 22 (25%) had primary lung cancer, 31 (35.2%) secondary breast cancer, 11 (12.5%) secondary esophageal cancer, 11 (12.5%) metastatic cancer and 13 (14.77 %) secondary stomach cancer.

The IL-17 level was 36.43±56.719 in males and 74.838±76.42 in females; and as a result of statistical analysis, no significant difference was observed for IL-17 levels in pleural fluid between males and female. Analysis of the mean pleural fluid protein levels was respectively 4373.8± 419.3 mg and 4411.7 ± 493 mg in the patients of MPE and BPE groups. There was a correlation between IL-17 and pleural fluid protein levels, but it was not statistically significant (r = 0.15). The mean IL-17 level was compared in smokers and nonsmokers, and statistical analysis showed no significant difference (P = 0.35). The results showed that 66 patients (50.8%) had a history of previous malignancy; 31 (46.97%) secondary to breast cancer, 11 (16.67%) secondary to esophageal cancer, 11 (16.67%) secondary to metastasis due to other causes and 13 (19.7%) secondary to stomach cancer had experienced MPE, and the mean IL-17 level was 63.9±36.6 in these subjects. In people who had no history of previous malignancy, including 22 (34.38%) with primary lung cancer and 42 (65.63%) with TB (totally 64 patients, 49.2%), the mean IL-17 level was 66.2 ± 75.5 in these people. Considering the higher mean IL-17 level in the group with no history of previous malignancy compared with the first group as well as P= 0.001, no statistically significant difference was observed for IL-17 levels between the two groups. The IL-17 level in pleural fluid of patients with MPE and BPE was respectively 69.73± 64.58 and 55.32±43.60; there was a statistically significant difference between the two groups (P = 0.02).

Differentiating between benign pleural effusion (BPE) and malignant pleural effusion (MPE) has remained controversial as a diagnostic issue. The majority of malignant pleural effusion (90% to 97%) is exudative type that occurs because of pleural membrane damage (Esther et al 1997). MPE can be seen as a complication in most malignancies, particularly in breast and lung cancer, while lung infections and tuberculosis cause the development of BPE.The gold standard for diagnosis of malignant pleural effusion is clinically the presence of malignant cells in pleural cells. Difficulty in differentiating between malignant and benign is the negative result of malignant cells in pleural fluid cytology. In these circumstances, differentiation from benign is problematic and the need for invasive measures such as thoracentesis is essential for the patient.

Closed pleural biopsy has less additional diagnostic value and thoracoscopy is the preferred method, since it is diagnostic in 90% of patients. However, there is no possibility of access to this invasive procedure in all centers. According to this issue, 130 patients with exudative pleural effusions were examined in this study. In the present study, 88 patients with malignant pleural effusion were compared with 42 patients with benign pleural effusion in terms of pleural fluid levels of IL-17. The patients were also evaluated for age, gender, history of previous cancer, smoking and pleural fluid protein levels. The mean age of subjects was close to each other in two age groups and no significant difference was found between the two groups. In addition, there was no statistically significant difference between IL-17 level and age of the patients.

In 2014, Chun Hua et al. examined a new biomarkers of interleukin 17 among 123 patients with exudative pleural effusion to determine the causes of pleural effusion. They showed that IL-17 level was significantly higher in MPE group compared with BPE group, similar to our results, and also stated that IL-17 can be used as a biomarker to differentiate MPE from BPE.

Since only one study has so far examined the level of IL-17 in pleural fluid, in addition to our study; so in the following discussion, we will consider similar studies closer to the present study, (Chun Hua et al., 2017).

Wang et al. in 2013 examined the levels of superoxide dismutase (SOD) in TPE and MPE, which was markedly higher in the TPE than the MPE. The results showed that SOD is not a suitable biomarker for these two types of pleural effusion (Xin-Feng Wang et al, 2013) In 2014, Chun Hua et al. examined serum levels of IL-17 in 128 patients with Non-small cell lung cancer (NSCLC). The results showed that higher levels of IL-17 in NSCLC group compared with the control group, which can be applied as diagnostic and prognostic value in patients with NSCLC.

Many studies have been conducted in the field of diagnostic value of cytology and the diagnostic value for diagnosing malignancies have been reported up to 70% in Iran. More invasive procedures such as biopsy, thoracoscopy or thoracotomy despite high sensitivity are not accepted through patients and physicians for diagnosis of tuberculosis and malignancies.

Therefore, researches in recent decades have led to find markers in pleural effusion and blood plasma to differentiate between tuberculosis and malignancies without invasion and with high-value and effectiveness of diagnosis and differentiation.

So far, only one study has examined the level of IL-17 in pleural effusion and high sensitivity has been

able to differentiate MPE than BPE. Like what mentioned above, other studies have been done on other biomarkers that some of them have been useful for the study. In our study, according to the significant differences for IL-17 levels in the two groups, its usability can be seen to differentiate between MPE and BPE. In addition, since the patients with primary lung cancer were in the group with no history of previous malignancy and the mean IL-17 was higher in these patients than in patients with secondary cancer as well as than TB, so significant difference was found between the two groups regarding history of previous cancer, though given limited studies done in this area and the lack of defined cut-off points, it definitely cannot be used as the only reference and diagnostic methods. Nevertheless, due to the apparent significant difference between the two groups, there is the possibility of using IL-17 beside other methods for differentiating malignant from benign diseases.

CONCLUSION

The results obtained from the present study demonstrated that age, gender, smoking, history of previous cancer and pleural effusion protein levels have no significant effect on IL-17 level. The IL-17 level was significantly higher in pleural effusion caused by malignant diseases than in exudative pleural effusion caused by benign diseases, especially tuberculosis.

Since the differentiation between malignant pleural effusion and benign pleural effusion, especially tuberculosis, sometimes needs to invasive procedures such as pleural biopsy or thoracoscopy, so it can be concluded that the IL-17 level regarding the significant difference can be used as a diagnostic approach in differentiating between the two types of pleural effusion.

It is recommended that the similar study should be conducted in different centers with larger sample size, as well as a variety of malignant and benign diseases can be studied separately.

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