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Use of pleural fluid C-reactive protein in diagnosis of pleural effusions

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The aims of the study were to assess whether C-reactive protein (CRP) is a sensitive marker for discriminating between transudative and exudative and pleural effusions to evaluate whether it can be used to distinguish inflammatory pleural effusions from other types of effusion.

Pleural fluid and serum CRP levels were obtained in 97 patients with pleural effusion, using an immunoturbidimetric method (Olympus AU-600 autoanalyser). We compared CRP levels between transudates and exudates, inflammatory effusions and other types of effusion.

According to the criteria used, 16 patients were included in the transudate group and 81 patients in the exudate group. Pleural fluid CRP levels were significantly lower in the transudate group ($P<0{\cdot}04$; $14{\cdot}9\pm4{\cdot}9$ mg l^{-1} and $35{\cdot}5\pm4{\cdot}9$ mg l^{-1} respectively). Also, the ratio of pleural fluid to serum was significantly lower in the transudate group ($P<0{\cdot}009$; $0{\cdot}8\pm0{\cdot}5$ mg l^{-1} and $2{\cdot}8\pm0{\cdot}7$ mg l^{-1}, respectively). In the exudate group, 35 patients had neoplastic effusions, 10 chronic non-specific pleurisy, 19 tuberculous pleurisy, 16 parapneumonic effusion and one Dressler Syndrome. When these sub-groups were compared, the parapneumonic effusion subgroup CRP levels (mean $89\pm16{\cdot}3$ mg l^{-1}) were significantly higher than those in the other subgroups, other exudate of neoplastic effusion, tuberculous pleurisy and chronic non-specific effusion and the transudate group ($P<0{\cdot}0001$; $P<0{\cdot}0001$; $P<0{\cdot}0004$ and $P<0{\cdot}0001$, respectively). The ratio between pleural fluid and serum CRP was significantly higher in the parapneumonic effusion subgroup than in the neoplastic subgroup ($P<0{\cdot}0002$; $6{\cdot}6\pm2{\cdot}7$ mg l^{-1} and $1\pm0{\cdot}2$ mg l^{-1}, respectively). Pleural fluid CRP levels >30 mg l^{-1} had a high sensitivity (93·7%) and specificity (76·5 %) and a positive predictive value of 98·4%. In the differential diagnosis of pleural effusions, higher CRP levels may prove to be a rapid, practical and accurate method of differentiating parapneumonic effusions from other exudate types. Although the high level of CRP obtained in the exudate group may be due to the number of patients with parapneumonic effusion who were included, the pleural CRP level may also be helpful in discriminating between exudative and transudative pleural effusions.

Key words: C-reactive protein; pleural effusion.

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Introduction

Measurement of C-reactive protein (CRP) levels is a clinically valuable screening test for organ disease, index of disease activity and measure of response to therapy (1). CRP levels have been shown to increase in a number of pulmonary diseases, notably bacterial infection, inflammation, neoplasia, pulmonary thromboembolism and some pleural effusions related to other conditions (1,2).

Assessing whether a pleural effusion is exudative or transudative in nature is the first step in determining its aetiology. Determining the cause of an exudative effusion is much more difficult than for a transudative effusion as CRP levels increase significantly in inflammatory effusions.

We investigated the diagnostic usefulness of pleural effusion CRP levels in the differential diagnosis of infectious pleural effusion and in discriminating exudative from transudative effusions.

Materials and methods

We carried out a prospective study on 97 patients (69 men, 28 women) with pleural effusion who were admitted to Atatürk Chest Disease and Surgery Center between May 1996 and March 1997.

Fasting blood samples and pleural fluid samples were obtained. The blood samples were centrifuged at 1500 ***g*** for 10 min. The pleural fluid samples were centrifuged at 2000 ***g*** for 10 min to remove blood and other matter. The serum

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and pleural fluid samples were stored at −25°C until CRP analysis.

The levels of glucose, total protein, albumin, lactic dehydrogenase (LDH) and adenosine deaminase (ADA) were measured in both sets of samples. Gram staining and aerobic and anaerobic culture were performed on the pleural effusion samples. To test for mycobacterium Ziehl Nielsen staining was performed after homogenization, then the samples were cultured in Loewenstein–Jansen culture media.

CRP analysis was performed on autoanalyser (Olympus AU-600, Tokyo, Japan) using an immunoturbidimetric method. The diagnostic reagent used for determination was GmBH (Hamburg, Germany; Normal value <5 mg l^{-1}; reference interval, 5–200 mg l^{-1}). According to the literature accompanying the test kit, its use was appropriate with both pleural and cerebrospinal fluid. The basic principle of the test is that when the fluid sample is mixed with the antiserum solution, the CRP reacts specifically with anti-human CRP antibodies to yield insoluble aggregates. The absorbance level of these aggregates is proportional to the concentration of CRP in the sample.

The patients were divided into two groups, transudative and exudative effusions using Light's criteria (3). Briefly, if one or more of the following criteria were present, the pleural effusions were classified as exudative: pleural fluid protein/serum protein ratio greater than 0·5; pleural fluid LDH/serum LDH ratio greater than 0·6; pleural fluid LDH greater than 200 IU l^{-1}. If the criteria were not met, the effusion was classified as transudative.

The diagnosis of tuberculous pleurisy was made by pleural biopsy and pleural fluid ADA levels of >70 IU l^{-1} were used to confirm this diagnosis. Criteria for the diagnosis of parapneumonic effusions were: positive aerobic or anaerobic culture; positive Gram stain; presence of a purulent effusion; white blood cell count of 5000–25 000; and neutrophil predominance. Malignancy was confirmed by a positive biopsy or cytology result. The one patient in the study who was diagnosed with Dressler Syndrome had experienced a myocardial infarction 3 weeks before admission to our hospital. The effusion was an exudative and the pathology report gave a diagnosis of non-specific pleuritis. The biopsy results for 10 other patients were chronic non-specific pleuritis (classified as the chronic non-specific pleuritis subgroup).

Statistical analysis was conducted using the Mann–Whitney U and Kruscal–Wallis tests.

Results

Of the study patients, 16 (16·4%) were included in the transudative effusion group, while 81 (83·6%) were included in the exudative effusion group. The exudative effusion group was further divided into five subgroups according to the diagnosis; parapneumonic effusions; tuberculous effusions; malignant effusions; chronic non-specific pleuritis; and Dressler Syndrome.

The distribution of the patients according to diagnosis and the mean, median, minimum and maximum values are given in Table 1 and Fig. 1.

Fluid CRP levels were significantly higher in exudative than in the transudative effusion group ($P<0·04$). In addition, the CRP levels in the parapneumonic effusion subgroup were significantly higher than in the neoplastic subgroup ($P<0·0001$), tuberculous pleurisy subgroup ($P<0·0001$), choronic non-specific pleurisy subgroup ($P<0·0004$) and the transudative effusion group ($P<0·0001$).

To determine the efficiency of pleural fluid CRP measurement in distinguishing exudative from transudative effusions, we had originally considered using a cut-off value of 30 mg l^{-1}. When this value was used, only two out of the 16 transudative effusion patients were grouped in the exudative effusion group. The sensitivity of the test was 93·7%, specificity 76·5%, and positive predictive value was 98·4%.

The ratio of pleural fluid to serum CRP was also significantly higher in the exudative effusion group than in the transudative effusion group ($P<0·003$). In addition, this ratio was significantly lower in the neoplastic effusion subgroup than in the parapneumonic effusion sub-group ($P<0·0002$)

Mean pleural CRP, serum CRP and pleural CRP/serum CRP ratio values for all groups are given in Table 2.

TABLE 1. Pleural fluid C-reactive protein levels in the study groups

	Transudative effusion	Exudative effusion	Malignant effusion	Parapneumonic effusion	Tuberculous effusion	Chronic non-specific pleuritis	Dressler syndrome
Patients (*n*)	16	81	35	16	19	10	1
Mean	14·9	35·5	22·9	89	26	12·8	
Median	10	22	11	64	11	6·5	
SD	19·6	44·2	22·4	65·2	29·2	14	
Minimum	1	1	1	22	2	1	26
Maximum	82	211	89	211	96	35	26

Data are given in mg l^{-1}

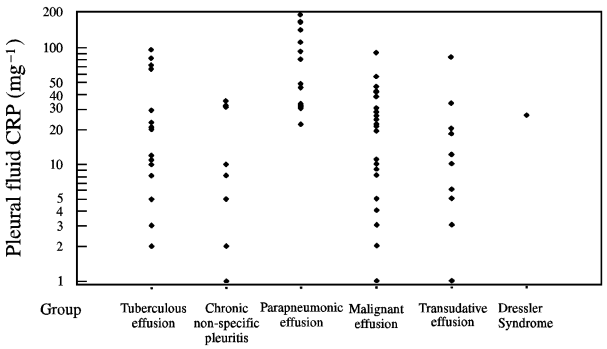

FIG. 1. Pleural fluid C-reactive protein levels in effusions secondary to transudative effusions, malignancy, pneumonia, tuberculosis and Dressler Syndrome. Each point represents one pleural fluid sample.

Discussion

In a living organism, a biochemical, physiological and immunological reaction cascade is produced as a response to chemical, physical and immunological stimuli, infectious agents and malignancies. This reaction is known as the acute phase response (4,5). CRP is an acute phase protein, synthesized by the liver in response to various stimuli (5). The induction of CRP synthesis is triggered by a number of cytokines which are released in the inflammatory region, chiefly the pirogenic cytokine, interleukin-6 (IL-6). The sources of IL-6 are fibroblasts, lymphocytes, promyelocytes and active macrophages (6,7).

CRP is thought to play an important role in inflammation, as it is seen to aggregate in the regions of inflammation where its level increases by 3000-fold, however, its *in vivo* function is not yet known. Two functions which have been reported to date are activation of the compleman system and recognition of molecules (8).

Classification of pleural effusions into transudative and exudative effusions is currently based upon Light's criteria (8). However, as these groups include many subtypes, the current classification does not solve the problem of diagnosis. In order to achieve a specific diagnosis, especially in the exudative effusion group, a more informative test is needed. Until now, measurements including bilirubin, cholesterol and ADA levels have been used with pleural fluid, but with no definite success (9,10).

Recently, many reports have been written on the biological use and the levels of CRP in numerous diseases, but few have focused on CRP levels in patients with pleural effusions (1,11,12). In this study, we aimed to assess the value of CRP levels in the differential diagnosis of exudate type, especially in the parapneumonic effusion subgroup.

Vidriales *et al.* (1) reported that CRP levels were highly elevated in inflammatory pleural effusions than in other types of effusion. We have obtained similar results in our study. They also reported that the pleural to serum CRP ratio was significantly elevated in exudative effusions and that this ratio was significantly lower in malignant effusions then in parapneumonic and tuberculosis effusions (1). Again, our findings confirm these results.

In our study, we found that serum CRP levels were similar in parapneumonic effusion subgroup to those in the other groups. Serum CRP levels are generally elevated in infectious states, but usually do not consistent across all bacteriaemic processes.

In tuberculous pleuritis, pleural effusion CRP levels are lower than those of parapneumonic effusions but as an indicator of inflammation they are higher than those found in transudative effusions (1,13).

Nakano *et al.* measured IL-6 and CRP levels in pleural effusions and serum from patients with mesothelioma, adenocarcinoma and tuberculosis. They found that CRP levels were similar in the mesothelioma and tuberculosis groups. However, Vidriales *et al.* found that CRP levels were twice as high in tuberculosis TB than in malignancy. The high CRP level which we found in malignancy in our study may have been due to the high number of mesothelioma patients included in our malignant subgroup and to the high levels of IL-6 found in malignant mesothelioma (7). Vidriales *et al.* used 10 mg l^{-1} as the cut-off value in their study (1), but we found that the cut-off value which yielded the best test performance was 30 mg l^{-1}. We therefore used this level as the cut-off value.

In conclusion, pleural fluid CRP levels may be used to discriminate parapneumonic effusions from other types of

TABLE 2. Mean pleural CRP, serum CRP and pleural CRP/serum CRP ratio values in all patient groups

Patient group	*n*	Pleural CRP level	Serum CRP level	Pleural CRP/serum CRP ratio
Transudative effusion	16	14.9 ± 4.9	54.8 ± 19.7	0.8 ± 0.5
Exudative effusion	81	35.5 ± 4.9	51.3 ± 7.4	2.8 ± 0.7
Malignant effusion	35	22.8 ± 3.7	35.8 ± 9.9	1 ± 0.2
Parapneumonic effusion	16	89 ± 16.3	69.4 ± 25.9	6.6 ± 2.7
Tuberculous effusion	19	26 ± 6.7	37.1 ± 11.5	2.9 ± 1.1
Chronic non-specific pleuritis	10	12.8 ± 4.4	22.7 ± 1.1	3.4 ± 1.7
Dressler Syndrome	1	26	21	1.2

Data are given in mg l^{-1} as means ± SD.

exudative effusion and may be helpful in distinguishing exudative from transudative effusions.

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