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ROLE OF PLEURAL FLUID C - REACTIVE PROTEIN IN PLEURAL EFFUSIONS

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ABSTRACT Pleural effusion is accumulation of fluid in the pleural space. It needs to be differentiated into transudate or exudate. The measurement of the C-reactive protein (CRP) may be useful in differentiating between transudative and exudative pleural effusions.

Aim: To study the Role of pleural fluid C-reactive protein in exudative versus transudative pleural effusions and to study whether it helps in etiological diagnosis.

Materials and Methods: Fifty patients with pleural effusion were enrolled. After signing the consent, detailed history and examination were done. Subjects were investigated according to the pre-designed proforma. CRP was analyzed by automated multichannel analyzer (Vitrios-350) in aspirated pleural fluid.

Results: In our study average pleural fluid CRP (mg/L) in transudates was 10 (mg/L). Average pleural fluid CRP of exudative group was 42 (mg/L). Tuberculosis patients had mean CRP of 51 (±23.4), parapneumonic effusions had mean CRP value of 29 (±12.9) while malignant effusions had CRP levels of 26 (±7.9). There was statistically significant difference for mean values of CRP between transudative and exudative pleural fluid effusions ($p<0.0001$).

Conclusion: C-reactive protein determination is simple, quick, inexpensive & easily available. Pleural fluid CRP level determination is highly significant test to distinguish between transudative and exudative pleural effusions (P=0.0001). CRP is also useful in establishing etiological diagnosis of pleural effusions. Higher CRP levels (>50mg/L)) are highly suggestive of tuberculosis while low CRP levels make this diagnosis unlikely. Pleural fluid CRP values were significantly higher in tuberculous than in parapneumonic, than that in malignancy and least in transudative effusion.

KEYWORDS : c - reactive protein (CRP), Pleural fluid effusion.

INTRODUCTION:

Accumulation of fluid in pleural space is called Pleural effusion. Pleural effusion occurs when fluid in the pleural space exceeds the normal physiological amount of 0.1-0.2 ml/Kg. Pleural effusion develops either when the formation of the pleural fluid is excessive and/or when the fluid reabsorption is disturbed. Pleural effusion may represent as a primary manifestation of many diseases, but most often they are observed as a secondary manifestation or complication of other disease and are of highly diverse etiology.

In evaluating a case of pleural effusion, important step is distinction between transudates and exudates. Transudates are formed by leakage of liquid across an intact barrier secondary to increase in osmotic pressure across that barrier. Exudates form from leakage of liquid and protein across an altered barrier with increased permeability and arise from injured capillary bed either in the lung, the pleura or adjacent tissues. Correctly categorizing pleural effusions limits the diagnostic possibilities.

The primary reason to differentiate between transudate and exudate is that, transudate will not require further intensive workup and therapy is directed to the underlying cause like congestive heart failure, cirrhosis of liver or nephrosis. Alternatively if the effusion proves to be an exudate, a more extensive diagnostic investigation is indicated.

The criteria proposed by Light et al in 1972 have been the standard method of differentiating exudates from transudates [1]. As per Light's criteria, a pleural effusion is exudate if one or more of the following criteria are met and transudate if none of the criteria is present.

- Ratio of pleural fluid protein to serum protein greater than 0.5.
- Ratio of pleural fluid LDH to serum LDH greater than 0.6.
- Pleural fluid LDH greater than 2/3rd the upper limit of normal for the serum LDH.

The thought for using the two different measurements is that the protein reflects the permeability of vessels where the fluid was formed while the LDH reflects the level of inflammation in the pleural space [(2)]. Light's criteria remains the best biochemical marker by which pleural effusion can be classified as transudates or exudates, but Light's criteria may misidentify many transudative effusions as an exudative. Several other tests have been proposed for the separation of transudates from exudates. Proposed tests included a pleural fluid cholesterol greater than 60mg/dl [3,4], a gradient of less than 1.2 g/dl for the difference between the serum and pleural fluid albumin level [5], pleural fluid to serum bilirubin ratio above 0.6 [6], pleural fluid viscosity [7], a high level of oxidative stress markers[8], soluble leukocyte selectin [9], various cytokines [10], uric acid [11], a pleural fluid to serum cholinesterase ratio above 0.23 [12], pleural fluid ADA [13], pleural fluid alkaline phosphatase [14].

C-reactive protein (CRP) level is clinically valuable screening test for inflammatory diseases [15,16]. Acute phase response is a general response to inflammation, triggered by cytokines, released from the sites from injury or inflammation [17]. C-reactive protein is an acute phase protein, produced in the liver & adipocytes. Increased production of this protein is triggered by cytokines, IL-6, TNF and IL-1, released by inflammatory cells [18]. A major function of C-reactive protein is the ability to bind phosphocholine and thus recognize some foreign pathogens as well as phospholipid constituents of damaged cells. It can activate complement system when bound to one of its ligand, and can also bind to phagocytic cells. It can also induce synthesis of inflammatory cytokines and tissue factor. C-reactive protein has many pathophysiological roles in inflammatory process [20]. Patients with tuberculous pleuritis tend to have much higher pleural fluid levels of C-reactive protein (CRP) than do patients with other lymphocytic pleural effusions. The advantage of the CRP test is that it is inexpensive and widely available.

METHODOLOGY AND RESULTS:

Institutional based prospective observational study was done. Patients with history and clinical examination. Suggestive of pleural effusions were included. Patients with frank empyema, hemothorax, post pleurodesis, chylothorax were excluded.

Data collection: A total of 50 cases were enrolled in the study. All the subjects were interviewed with detail history and underwent examination and investigated according to the proforma that was pre-designed and pre tested. Informed consent was secured from the patients for participation in the study. Besides routine investigations of

hemogram with ESR, serum biochemistry, all the patients were subjected to the chest radiography (PA view),sputum gram stain, sputum AFB stain, pleural fluid analysis for total count and differential count, pleural fluid chemistry, pleural fluid AFB stain, pleural fluid gram stain and pleural fluid cytology. Pleural fluid and venous blood were simultaneously drawn for biochemical parameters of proteins, albumin, LDH and CRP. Biochemical analysis was done by multichannel analyzer (Vitrios 350) after thorough calibration of the analyzer. Total count and differential count of pleural fluid were done manually.

Pleural effusions can be differentiated into transudative or exudative by comparing chemistries in the pleural fluid. The measurement of C-reactive protein 'CRP' (one of acute phase reactants) may be useful in differentiating between transudative and exudative pleural effusions.

Observations: In our study, 52%(26) of the patients were between 30-60 years followed by 28%(14) patients were in age group <30, and 20%(10) were in the age group >60yrs.Mean age of the patients was 43yrs with standard deviation of ± 17.6 In our study, males constituted 66% of total patients, 34% of them were females. Out of 50 pleural effusions, 21 were on right and 21 were on left side while 8 were bilateral. Seven out of 8 bilateral effusions were transudates.

Among the 50 patients 7 patients were diabetic, 7 hypertensives, 7 had ischemic heart diseases, 7 were suffering from renal disease and about 3 patients were suffering from COPD.

In the study population of 50 cases with pleural effusion, 33 patients were male and 17 patients were females out of which 8 male patients had tubercular effusion, 8 had parapneumonic effusion, 4 had malignancy, 3 had congestive cardiac failure and 5 patients were suffering from renal disease. Among females 5 patients had tuberculosis, 4 had parapneumonic effusion, 3 had malignancy, 1 had congestive cardiac failure and 1 was suffering with chronic renal failure. Others included HIV, pancreatitis, ILD, Connective tissue disease & hypertension.

Distribution of cases according to the etiology and Light's criteria

Exudate: In our study of 50 patients; 35 patients were classified as exudates according to the gold standard Light's criteria. In our study commonest cause of exudative effusion was tuberculosis 37% , parapneumonic effusion constituted 30% while 21% exudates were malignant.

Transudate: In our study of 50 patients; 15 patients were classified as transudates according to the gold standard Light's criteria. In our study, 20% (10) transudative effusions were secondary to cardiac failure and 30% were secondary to chronic renal disease. While hypertensive, synpneumonic and others constituted the rest.

Distribution of pleural fluid C-Reactive protein according to etiological groups:

EXUDATE: In our study average pleural fluid CRP (mg/L) of exudative group was 42 ±19.07.Tuberculosis patients had mean CRP of 51 (±23.4) , parapneumonic effusions had mean CRP value of 29 (±12.9) while malignant effusions had CRP levels of 26 (±7.9)

TRANSUDATES: In our study average pleural fluid CRP (mg/L) of transudative group was 10 ±6.3.

All groups except chronic kidney diseases had average CRP levels less 10. CKD patients had mean CRP level of 14 with standard deviation of ±8.1. (Refer figure 1).

As evident from the above scatter diagram, pleural fluid CRP levels in majority of transudative effusions lie below 10 mg/L whereas in majority of exudative effusions it lies above 20mg/L.

ROLE OF PLEURAL FLUID C REACTIVE PROTEIN IN ETIOLOGICAL DIAGNOSIS OF PLEURAL EFFUSIONS:

First step during diagnostic workup of any effusion is to differentiate transudative Vs exudative effusion. As evident from the scatter diagram below in our study, pleural fluid CRP levels in majority of transudative effusions are below 10 mg/L.

Following graph distribution(figure 2) of pleural fluid CRP value in our study population.

C-reactive protein (CRP) in pleural fluid has been found to be higher in tuberculosis and parapneumonic effusions than in other causes of pleural effusion. Earlier studies have shown the diagnostic accuracy (sensitivity, specificity) of CRP in pleural fluid for diagnosing tuberculosis at different cut-off points. A CRP level of < 30 mg/l virtually ruled out the possibility of tuberculosis as the cause of a lymphocytic pleural effusion (sensitivity 95%).

A specificity of > 90% for diagnosing tuberculosis was obtained at a CRP value >45 mg/l. Our study results showed mean value of 51 mg/l with standard deviation of ±23.4 in 13 patients with tuberculous pleural effusions. Higher CRP levels are strongly associated with diagnosis of tuberculosis.

SENSITIVITY & SPECIFICITY OF PLEURAL FLUID C-REACTIVE PROTEIN FOR DIAGNOSING TRANSUDATIVE EFFUSION:

Sensitivity and specificity together with predictive accuracy are inherent properties of screening test. These are discussed below in table 1– By taking cutoff value of 10mg/L for diagnosing transudates the sensitivity, specificity, Positive Predictive Value and Negative Predictive Value is as follows. (Refer table 2).

By applying unpaired student "t-test" , the standard error of difference between the two means is 8.86 The actual difference between two means is 32, which is more than twice the standard error of difference between the two means and therefore significant (P<0.05). . (Refer table 3).

CONCLUSION

- It was found in our work that pleural fluid CRP levels were significantly higher in benign exudates than in malignant exudates and pleural fluid CRP in tuberculous effusion was significantly higher in comparison to that in malignant & parapneumonic effusions.
- Our study results showed mean value of 51 mg/l with standard deviation of ±23.4 in 13 patients with tuberculous pleural effusions. Higher CRP levels are strongly associated with diagnosis of tuberculosis.
- C-reactive protein (CRP) is an acute-phase protein widely used as a marker of inflammation and tissue injury. Its determination is simple, quick and inexpensive & easily available. Pleural fluid CRP level determination is highly significant test to distinguish transudative and exudative pleural effusions and also useful in establishing etiological diagnosis of pleural effusions. Higher CRP levels (>50mg/l)) are very suggestive of tuberculous pleuritis, and low CRP levels make this diagnosis unlikely.

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