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An Evaluation of Levels of C - reactive protein in Serum and Pleural Fluid of Pleural Effusion of Different Etiology

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Background: *Pleural effusion is an abnormal accumulation of fluid in the pleural cavity influencing the respiratory process in causing difficulties in the normal movement of the lungs. Pleural effusion is caused by a variety of diseases, including pulmonary infections, pleural tumour metastasis and tuberculous pleurisy.*
Objective: *To investigate the diagnostic usefulness of pleural effusion CRP levels in the differential diagnosis of infectious pleural effusion and in discriminating exudative from transudative effusions.*
Material and methods: *This was a cross-sectional study carried out in patients admitted in medicine ward and outdoor clinics of a tertiary care hospital in north India. The study comprised of fifty two patients of pleural effusion which satisfied the inclusion criteria. The patients age> 14 years, clinical & radiological evidence of pleural effusion were included in the study. Detailed history, thorough physical examination, radiological findings, haematological and biochemical findings were evaluated. Pleural aspiration was performed on all patients. Biochemical analysis of pleural fluid were performed in all patients including C-reactive protein levels.*
Results: *Out of the total pleural effusion cases, 46.1% were tubercular, 25% were transudative, 15.4% were malignant and 13.5% were parapneumonic. Left site of pleural effusion was in 85.7% of parapneumonic and 75% of Tubercular. The one way analysis of variance revealed that there was significant ($p<0.01$) difference in the level of C-reactive protein among different types of pleural effusions. The post-hoc analysis showed that C-reactive protein was found to be significantly ($p=0.01$) different among all the types of pleural effusions.*
Conclusion: *Pleural fluid CRP levels in exudative effusion were significantly higher than transudative effusion. There was also significant increase in inflammatory effusion when compared to non-inflammatory effusion.*
Keywords: *pleural effusion, C-reactive protein, Diagnostic usefulness*

I. Introduction

Pleural effusion is an abnormal accumulation of fluid in the pleural cavity influencing the respiratory process in causing difficulties in the normal movement of the lungs. In this case, the pleural fluid formation is over passing its rate of absorption, and the pleural cavity has an exaggerated amount of pleural liquid in compare its normal state (Light, 2002). Based on Light's criteria and on biochemical, cytological and microbiological analyses can be possible in evaluating an exudative pleural effusion. Once the possible exudative pleural effusion is set up it is needed to determine the etiology of the effusion. The common causes for an exudative pleural effusion are malign, parapneumonic and tuberculosis (Hakani and Mitre, 2016).

Pleural effusion is caused by a variety of diseases, including pulmonary infections, pleural tumour metastasis and tuberculous pleurisy (Porcel, 2009; Light, 2011) and the latter two diseases remain difficult to differentiate in clinical practice. The aetiological diagnosis of pleural effusion is extremely important for the treatment and prognosis of patients. Therefore, highly sensitive and specific biomarkers that are convenient and applicable for the differential diagnosis of pleural effusions are urgently needed.

Adenosine deaminase (ADA) is an enzyme associated with T lymphocyte activity and is produced from all the cells of human body but its level are higher in lymphocytes.6 ADA plays an important role in the differentiation and maturation of the lymphoid system. C-reactive protein (CRP) is a protein of acute phase inflammation that is produced by liver and is present in the body before the antibodies (Hakani and Mitre, 2016).

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 (Castan et al, 1992). 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 (Castan et al, 1992; Mith and Lipworth, 1995).

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 (Turay et al, 2000).

This study was designed to evaluate the diagnostic usefulness of pleural effusion CRP levels in the differential diagnosis of infectious pleural effusion and in discriminating exudative from transudative effusions.

II. Material And Methods

This was a cross-sectional study carried out in patients admitted in medicine ward and outdoor clinics of a tertiary care hospital in north India. The study was approved by the Ethical Committee of the Institute. The consent was taken from each participant before including in the study.

The study comprised of fifty two patients of pleural effusion which satisfied the inclusion criteria. The patients age> 14 years, clinical & radiological evidence of pleural effusion were included in the study. The patients with aged>65 year, pleural effusion of trauma were excluded from the study.

Detailed history, thorough physical examination, radiological findings, haematological and biochemical findings were evaluated. Pleural aspiration was performed on all patients. Biochemical analysis of pleural fluid were performed in all patients including C-reactive protein levels.

Biochemistry of pleural fluid: Determination of pleural fluid total proteinconcentration (g/l), LDH(U/L) and sugar (mmol/l) were performed. To differentiate transudate from exudate, the ratio of pleural fluid and serum protein ;the ratio of pleural fluid and serum LDH were calculated. Pleural fluid Adenosine deaminase level was measured by Giusti and Galanti method.

C-reactive protein in pleural fluid were measured by immunoturbidimetric method by using kit. The test is based on the principle of agglutination reaction between latex reagent and C-reactive protein to form insoluble complex. Transudative and exudative pleural effusion was distinguished by measuring the LDH and protein level in the pleural fluid.

Statistical analysis

The results are presented in mean±SD and percentages. The one way analysis of variance (ANOVA) followed by Tukey's post hoc tests was used to compare the continuous variables among the different types of pleural effusion. The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

III. Results

Out of the total pleural effusion cases, 46.1% were tubercular, 25% were transudative, 15.4% were malignant and 13.5% were parapneumonic. Left site of pleural effusion was in 85.7% of parapneumonic and 75% of Tubercular. However, right site was in 46.2% of transudative pleural effusion (Table-1).

The pleural effusion was found to be most common in the age 26-35 years (28.8%) followed by 12-25 & 36-45 (21.2%), 46-55 (19.2%) and 56-65 (9.6%) years. Majority of the pleural cases were males (73.1%) (Table-2).

The one way analysis of variance revealed that there was significant (p=0.0001) difference in the level of haematological parameters among different types of pleural effusions. The post-hoc analysis showed that Hb level was significantly different between transudative and parapneumonic (p=0.0001) as well as between parapneumonic and malignant (p=0.0001). However, TLC was found to be significantly (p=0.0001) different among all the types of pleural effusion. ESR was also found to be significantly (p=0.0001) different between tubercular and transudative & malignant (p=0.0001) (Table-3).

The one way analysis of variance revealed that there was significant (p<0.01) difference in the level of pleural fluid protein, sugar and LDH among different types of pleural effusions. The post-hoc analysis showed that protein & sugar level was significantly different between transudative and parapneumonic (p=0.01). However, LDH was found to be significantly different among all the types of pleural effusions (Table-4).

The one way analysis of variance revealed that there was significant (p<0.01) difference in the level of C-reactive protein among different types of pleural effusions. The post-hoc analysis showed that C-reactive protein was found to be significantly (p=0.01) different among all the types of pleural effusions (Table-5).

IV. Discussion

Pleural effusion occurs secondary to either systemic causes or disease of pleura.Conventional non invasive diagnostic methods are not always accurate in establishing the diagnosis of pleural effusion. Analysis of pleural fluid yields important information in early differential diagnosis of pleural effusion. Standard workup

analysis of pleural fluid includes differentiatingwhether pleural fluid is transudative or exudative. For many years the most accepted criteria for discriminating transudative from exudative pleural effusion is Light's criteria.However Light's criteria may differentiate certain transudative effusion as exudative effusion.

The most important cause of transudative pleural effusion is cardiac failure. TB is the leading cause of preventable morbidity and mortality from an infective agent and tuberculous effusion is important treatable cause of exudative pleural effusion. Other common causes of exudative effusions are malignancy, parapneumonic pleural effusions, connective tissue disorders, fungalinfections etc. Various biological markers have been investigated in the diagnosis of pleural effusion. Among these pleural fluid ADA, CRP, interferon γ, cytokines, interleukins, tumour markers, vascular endothelial growth factor have been found to be of value in the differential diagnosis of pleuraleffusion. Nevertheless many of these markers have limited value, either because of low sensitivity &specificity or high cost.

The diagnosis of tuberculous pleural effusion is difficult because of low sensitivity and specificity of various non invasive tools like acid fast bacilli staining, culture of pleural tap andtuberculin skin testing. Diagnosis increases to 96.2% with pleural biopsy but the disadvantage of it's invasiveness.

In a report by Garcia et al (2005), a patient with mesothelioma had high ADA level (73U/L) and CRP concentration of 8.9mg/L and they reviewed that elevated levels of ADA are seen in approximately a third of mesothelioma patients. In the present study a patient diagnosed as mesothelioma had ADA level of 61U/L and CRP level was 0.8mg%.

In another study by Jimenez et al (2003) on ADA levels in non tuberculous pleural effusion, a negative predictive value of 99% was reported for diagnosis of non tuberculous pleural effusion and the ratio of ADA1/ADA2 correctly classified all the cases as non tuberculous pleural effusion.ADA exists in two isoenzyme forms, ADA1 is expressed in all cells where as ADA2 is found only in monocytes.

C - reactive protein is another sensitive marker in distinguishing the diagnosis of pleural effusion. It is widely used as a maker of inflammation and tissue injury. CRP levels have been found higher in benign than malignant pleural effusion. High pleural fluid CRP levels have been reported in tuberculous pleural effusion and PPE.

In the present study, CRP levels were lowest in transudative effusion when compared to exudative effusion which was highly significant ($p<0.001$). A high significant increase was seen in inflammatory pleural effusion (tuberculous effusion and PPE) when compared to non inflammatory effusion (transudative and malignant effusion) ($p<0.001$). Tuberculous pleural effusion had high CRP levels when compared to transudative and malignant pleural effusions which were highly significant. But the highest values were found in PPE which was highly significant when compared with transudative effusion, tuberculous effusion and malignant effusion.

Yilmaz et al (2000) reported high levels of CRP in exudates when compared to transudates and high levels in parapneumonic pleural effusions when compared to other types of exudative pleural effusions and also reported high sensitivity (93.7%), specificity (76.5%) and PPV of 98.4% at a cutoff value of 30mg/L. A similar finding was also reported by Castano and Amores (1992) in which good sensitivity (82%), specificity (87.5%) and PPV (95.5%) in diagnosis of exudative pleural effusion was found.

Hoda et al (2010) showed high values of CRP in exudative pleural effusions when compared to transudative pleural effusions. However in their study tuberculous effusion had statistically higher CRP levels when compared to malignant pleural effusions and parapneumonic pleural effusions.

Pleural fluid CRP levels have also been useful in discriminating uncomplicated parapneumonic pleural effusions from complicated parapneumonic pleural effusions and empyema. High levels of CRP have been found in complicated PPE and very high levels are seen in empyema cases as in other studies (Chierakul et al, 2004; Nakano et al, 1998; Kapisyzi et al, 2009; Pepys and Hirschfield, 2003; .

Daniil et al (2007) evaluated multiple biomarkers in discriminating pleural effusion. They concluded the combination of ADA and CRP levels might be sufficient in discriminating the three different groups of pleural effusion, tubercular, malignant and PPE. The estimation of ADA level in pleural fluid is very helpful in establishing the etiology of tubercular pleural effusion and to rule out non tubercular pleural effusion. Pleural fluid ADA can be utilized for differentiating tuberculosis effusions from those of non-tuberculosis etiology, this is confirmed in other studies (Mehta et al, 2014).

In the present study, in most cases of tuberculous pleural effusion the ADA levels were >40U/L and CRP levels >2mg/dl, in PPE the ADA levels were <40 U/L (except empyema cases) and CRP levels >6mg/dl, where as in both malignant and transudative and CRP levels <2mg/dl. The present study is in accordance with findings of Daniil et al (2007).

V. Conclusion

Pleural fluid CRP levels in exudative effusion were significantly higher than transudative effusion. There was also significant increase in inflammatory effusion when compared to noninflammatory effusion.

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Table-1: Distribution of pleural effusion and site of effusion

Type of PE	Site						Total	
	Left		Right		Bilateral			
	No.	%	No.	%	No.	%	No.	%
Tubercular	18	75.0	4	16.7	2	8.3	24	46.1
Transudative	0	0.0	6	46.2	7	53.8	13	25.0
Malignant	6	75.0	1	12.5	1	12.5	8	15.4
Parapneumonic	6	85.7	1	14.3	0	0.0	7	13.5
Total	30	57.7	12	23.1	10	19.2	52	100.0

Table-2: Age and sex distribution of pleural effusion cases

Age and sex	No. (n=52)	%
Age in years		
15-25	11	21.2
26-35	15	28.8
36-45	11	21.2
46-55	10	19.2
56-65	5	9.6
Sex		
Male	38	73.1
Female	14	26.9

Table-3: Haematological parameters in pleural effusion cases

Type of pleural effusion	No. of cases	Hb%	Total Count	ESR
Tubercular	24	9.61±0.817	7800.00±900.00 [a]	68.00±13.09[a, b]
Transudative	13	8.61±1.49[a]	7000.00±1500.00 [a]	15.7±5.68 [a, c]
Malignant	8	8.41±0.95[b]	8000.00±1300.00 [a]	45±13.16 [a]
Parapneumonic	7	11.76±0.97 [a,b]	12500.00±1500.00 [a]	41.6±10.8[b,c]
ANOVA p-value		0.0001*	0.0001*	0.0001*

[a,b,c]p=0.0001 (Post hoc tests), *Significant

Table-4: Distribution of pleural fluid protein, sugar and LDH level in different groups of pleural effusion

Type of Pleural effusion	Protein (gm%) Mean ± SD	Sugar (mg%)Mean ± SD	LDH(U/L) Mean ± SD
Tubercular	4.9 ± 0.92	59.1 ± 11.24	139 ± 51.6 [a]
Transudative	2.1 ± 0.39[a]	67.8 ± 13.41 [a]	85.5 ± 27.9 [a]
Malignant	4.7 ± 0.41	44.3 ± 11.26	253.5 ± 139.7 [a]
Parapneumonic	5.1 ± 0.79[a]	48.0 ± 7.83 [a]	180 ± 78.2 [a]
ANOVA p-value	0.001*	0.001*	0.0001*

[a]p=0.01 (Post hoc tests), *Significant

Table-5: Pleural fluid C-reactive protein level in different type of pleural effusion

Type of Pleural effusion	C-reactive protein (mg/dl) Mean ± SD
Tubercular	3.21 ± 0.81[a]
Transudative	0.80 ± 0.42 [a]
Malignant	1.21 ± 1.05 [a]
Parapneumonic	7.32 ± 0.98 [a]
ANOVA p-value	0.001*

[a]p=0.01 (Post hoc tests), *Significant