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ORIGINAL ARTICLE

VALUE OF C-REACTIVE PROTEIN IN ETIOLOGIC DIAGNOSIS OF PLEURAL EFFUSION

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Background: ***Pleural effusion means abnormal accumulation of fluid in the pleural space. It can be differentiated into transudative or exudative by comparing chemistries in the pleural fluid to those in the blood. The measurement of C-reactive protein 'CRP' (one of acute phase reactants) may be useful in differentiating between transudative and exudative pleural effusions.***

Aim of the Work: ***Study of C-reactive protein in exudative versus transudative pleural effusions, and does it have a diagnostic value?***

Subjects and Methods: ***This study was conducted on forty patients who had pleural effusion in the departments of chest in Kasr El -Aini Hospitals, their age ranged between 11 to 70 years; patients were assigned into four groups: Group I: Ten patients with transudate pleural effusion (due to liver cirrhosis); group II: Twelve patients with tuberculous pleural effusion; group III: Fourteen patients with malignant pleural effusion; group IV: Four patients with bacterial cause parapneumonic pleural effusion. Thorough clinical history; chest X-ray, CT of chest and abdominal ultrasound for some cases. Tuberculin skin test, liver & renal functions. Serum and pleural fluid measurement of LDH, adenosin deaminase, glucose, total proteins and albumin; CRP was analyzed by turbidiameters in aspirated pleural fluid and in serum, pleural biopsy was done according to the case.***

Results: The current study revealed a highly significant increase of CRP level in serum and pleural fluid in bacterial pneumonia, tuberculous pleurisy, pleural mesothelioma. Fluid CRP levels were significantly higher in exudative than in transudative effusions, also pleural fluid CRP levels were significantly higher in benign exudates than in malignant exudates. **Conclusion:** ***High CRP levels are very suggestive of tuberculous pleuritis, and low CRP levels make this diagnosis unlikely. Fluid CRP values were significantly higher in tuberculous more than in malignancy, than that in parapneumouic and least in transudative effusion.***

Keywords: ***C-rcactive protein, Exudative, Transudative pleural effusions.***

INTRODUCTION

The pleural surfaces, lined by mesothelial cells, are subject to injury by substances and cells brought to them via the blood stream or by lymphatic vessels or inadvertently introduced from without, as by penetrating wounds. Injury often subtle or even convert, may elicit responses ranging from inflammatory to neoplastics.(6)

Pleural effusion is an abnormal accumulation of fluid in the pleural space, and it is a common problem in clinical

practice. It can be caused by several mechanisms, increased permeability of pleural membrane, increased pulmonary capillary pressure, decreased negative intrapleural pressure, decreased oncotic pressure and obstruction of lymphatic flow.[16]

The differentiation between exudates and transudates is fundamental when investigating the cause of pleural effusions, transudative and exudative pleural effusions are differentiated by comparing chemistries in the pleural fluid to those in the blood. According to a meta-analysis, exudative pleural effusions meet at least one of the following criteria Pleural fluid protein >2.9 g/dL, pleural fluid cholesterol >45 mg/dL (1.16 mmol/L), and lastly pleural fluid LDH >60 percent of upper limit for serum whereas transudative pleural effusions meet none.[7]

C-reactive protein (CRP) is a member of the class of acute-phase reactants as its levels rise dramatically during inflammatory processes occurring in the body. This increment is due to a rise in the plasma concentration of IL-6, which is produced predominantly by macrophages as well as adipocytes. CRP binds to phosphocholine on microbes. It is thought to assist in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages, which express a receptor for CRP. It is also believed to play another important role in innate immunity, as an early defense system against infections.[11]

Malignancy is the second most common cause of exudative pleural effusions with lung cancer (36%), breast (25%) and lymphoma (10%) being the most frequent causes. Typical pleural fluid characteristics include a mononuclear predominant exudate (average 2500 cells/mm3), with an average red blood cell count of 40,000 cells/mm3, normal glucose (>60 mg/dl) and positive cytology. At the time of diagnosis one- third of patients have a low pleural fluid glucose (<60 mg/dl), which is associated with more extensive disease and a poorer prognosis.

Nitipatana et al. (2004) concluded in their study that in patients presenting with lymphocytic exudative pleural effusion, a simple marker of raised pleural fluid CRP level may be helpful in discriminating between tuberculous pleural effusion and malignant pleural effusion. CRP pleural fluid level determination is useful in the diagnostic workup of lymphocytic pleural effusions. High CRP levels are very suggestive of tuberculous pleuritis, and low CRP levels make this diagnosis unlikely.[5,17]

Also, measurement of pleural CRP can be useful in the workup of patients with a parapneumonic effusion in order to differentiate complicated parapneumonic pleural effusion from uncomplicated parapneumonie pleural effusion.[3,5]

It was hypothesized that measurement of CRP may be useful in differentiating between transudates and exudates and between benign and malignant effusion. Kiropoulos et al. (2007) concluded in their study that pleural CRP level provides useful information for the study of pleural exudates. A level below 20 mg/L suggests a malignant origin and a level above 45 mg/L virtually rules out this possibility.

Aim of the study:

- Study of C-reactive protein in exudative versus transudative pleural effusions;
- Does CRP have a diagnostic value?

PATIENTS AND METHOD

Forty patients who had pleural effusion. Patients were selected from Chest Departments El Kasr Al-Eini (Cairo University). Each subject signed in a special form consent that will be written in simple phrase. The procedure and the aim of the work were explained to all subjects in simple.

Subjects were divided into four groups:

- ***Group I:*** Ten patients with transudate effusion due to hypoalbuminaemia (liver cirrhosis), their age ranged from 42-76 years;
- ***Group II:*** Twelve patients with tuberculous effusion, their aged ranged from 21-56 years;
- ***Group III:*** Fourteen patients with malignant effusion, their age ranged from 61-70 years;
- ***Group IV:*** Four patients with bacterial cause parapneumonic pleural effusion, their age ranged from 11-70 years.

All subjects will be submitted fox:

1. Thorough clinical history including smoking and occupational histories;
2. Full general and local clinical examination;
3. Radiographical investigations: Plain chest X-ray postero-anterior and lateral views, CT of chest when indicated, and abdominal ultrasound for some cases;
4. Routine laboratory tests including: CBC, ESR tuberculin skin test (5 units of P.P.D. in 0.1 ml. intra-dermal), liver functions (ALT, AST, s. bilirubin), renal functions (s. urea and s. creatinine); serum LDH, adenosin deaminase (ADA), glucose total plasma proteins and albumin:
   - Fresh blood sample and maximum one week at 2°C was submitted for:
   - Serum was separated from the clot and analyzed.

- CRP was analyzed by turbidiameters in machine (CBAS, INT, GRA400).
- Method Particle enhanced immunoturbidimetry.
- Principle: Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The participate is determined turbidimetrically at 5.52 nm.

5. Aspiration of pleural fluid was done and was sent immediately for the following:
   - Biochemical examinations including: protein content, sugar level, LD.H., A.D.A.; Cytological examination of the fluid; Bacteriological examination:
   - Gram staining and culture were performed; C-reactive protein measurement in pleural fluid: 2 ml of fresh pleural fluid was analyzed.
6. Tissue biopsy: One of the following methods was done according to the case: Thoracoscopic pleural biopsy; CT guided biopsy; Abram's needle pleural biopsy; Transbronchial lung biopsy using fibro-optic bronchoscopy; Open lung biopsy.

Transudative and exudative pleural effusions are distinguished by measuring the lactate dehydrogenase (LDH) and protein levels in the pleural fluid. Exudative pleural effusions meet at least one of the following criteria, whereas transudative pleural effusions meet none:

1. Pleural fluid proteinlserum protein ratio >0.5
2. Pleural fluid LDH / serum LDH >0.6.
3. Pleural fluid LDH more than two-thirds normal upper limit for serum.

The diagnosis of tuberculous pleurisy was based on high tuberculin positivity, lymphocytic pleural fluid, few mesothelial cells, adenosine deaminase (ADA) level in pleural fluid or pleural biopsy showing caseating granuloma.

Effusions were considered malignant if malignant cells were found on cytological examination of pleural fluid or in the pleural biopsy specimens, whether thoracoscopic, by using Abram's needle or open lung biopsy.

Parapneumonic effusion was diagnosed on the bases of: Clinical, biochemical and radiological signs suspected acute inflammation, positive Gram staining, positive culture for bacteria or neutrophil cells predominance in pleural effusion.

RESULTS

The present study was carried out in Chest departments of El Kasr Al-Eini, Cairo University, in the period between May 2008 to November 2008. Forty patients were included in this study and were divided into 4 groups:

- ***Group I:*** Ten patients with transudate pleural effusion;
- ***Group II:*** Twelve patients with tuberculous pleural effusion.
- ***Group III:*** Fourteen patients with malignant pleural effusion.
- ***Group IV:*** Four patients with bacterial cause parapneumonic pleural effusion.

Table 1. Demographic data of all patients.

		Exudates (n=30)			Transudate	Total
		Malignant	T.B	Parapneumonic		
Number		14 (35%)	12 (30%)	4 (10%)	10 (25%)	40 (100%)
Age (years)	Mean	53.58	33.3	40.98	54.0	
	± S.D	±14.98	±10.26	±24.30	±9.0	
Sex	Male	10	9	2	6	27 (67.5%)
	Female	4	3	2	4	13 (32.5%)
Smoking (cigarette)	Smoker	5	6	1	6	18 (40%)
	Ex-smoker	1	1	0	0	2 (10%)
	Non-smoker	8	5	3	4	20 (50%)

Table 2. Statistical analysis for age of patients with different types of exudative pleural effusion.

Items	Mean ± S.D
Malignant (n=14)	53.58 ± 14.98
T.B (n=12)	33.33 ± 10.26
Parapneumonic (n=4)	40.98 ± 24.31
t-test	6.21
p-value	<0.006
Significant	H.S

S.D = Standard Deviation; *p* = Probability value; < = Less than.

Table 2. It was observed that there was highly statistically significant difference between mean values of age among patients with different types of exudative pleural effusion ($p<0.006$).

Table 3. Shows the mean values of protein level in pleural fluid, serum and fluid to serum ratio among transudative and exudative effusion.

		Trasudatives (n=10)		Exudative (n=30)		t-test	p-value	Sig.
		Mean	±S.D	Mean	±S.D			
Protein	Pleural fluid	0.92	±0.22	4.38	±1.36	7.95	0.001	H.S
	Serum	2.34	±0.37	6.65	±2.37	5.69	0.001	H.S
	F/S	0.40	±0.08	0.69	±0.18	4.77	0.001	H.S

S.D = Standard Deviation; p = Probability value; < = Less than.

Table 3. It revealed that there was statistically high significant difference between mean values of protein level in pleural fluid serum and fluid to serum ratio among transudative and exudative pleural effusion ($p<0.001$).

Table 4. Shows CRP in pleural fluid serum and fluid to serum ratio, comparison between transudative and exudative effusion.

		Trasudatives (n=10)		Exudative (n=30)		t-test	p-value	Sig.
		Mean	±S.D	Mean	±S.D			
CRP	Fluid	0.30	±0.11	2.64	±2.36	3.136	<0.003	H.S
	Serum	2.15	±1.19	6.76	±6.74	2.137	<0.039	S
	F/S	0.14	±0.11	0.39	±0.34	1.408	>0.167	N.S

S.D = Standard deviation; P = Probability value; Sig. Significant; < = Less than; > = more than.

There was statistically high significant difference for mean values of CRP between transudative and exudative pleural fluid effusion ($p<0.003$).

There was statistically significant difference of CRP in serum between transudative and exudative effusion ($p<0.039$). There was no statistically significant difference of CRP in fluid to serum ratio between transudative and exudative effusion ($p>0.167$).

Table 5. Shows CRP in pleural fluid, serum and fluid to serum ratio among subtypes of exudative effusion.

		T.B (n=12)		Malignancy (n=14)		Parapneumonic (n=4)		F-test	p-value	Sig.
		Mean	±S.D	Mean	±S.D	Mean	±S.D			
CRP	Fluid	3.93	±2.73	1.91	±1.71	1.35	±1.91	3.655	<0.039	S
	Serum	7.09	±5.83	8.20	±7.69	0.78	±6.40	2.46	>0.140	NS
	F/S	0.55	±0.47	0.23	±0.21	1.73	±1.30	1.714	>0.199	NS

S.D = Standard deviation; F = Distribution; P = Probability value; Sig. Significant; < = Less than; > = more than.

Table 5 showed that there was statistically significant difference between mean values of CRP in subtypes of exudative pleural fluid effusions (p<0.039).

There was no statistically significant difference between mean values CRP in serum and fluid to serum ratio for subtypes of exudative effusions (p>0.140) and (p>0.l99) respectively.

Table 6. Shows the mean values of CRP in pleural fluid, serum and fluid to serum ratio among four types of effusion.

		Transudative (n=10)		T.B (n=12)		Malignancy (n=14)		Parapneumonic (n=4)		F-value	p-value	Sig.
		Mean	±S.D	Mean	±S.D	Mean	±S.D	Mean	±S.D			
CRP	Fluid	0.30	±0.11	3.93	±2.73	1.91	±1.71	1.35	±1.91	7.191	<0.001	H.S
	Serum	2.15	±1.19	7.09	±5.83	8.20	±7.69	0.78	±6.40	3.457	<0.020	H.S
	F/S	0.14	±0.11	0.55	±0.47	0.23	±0.21	1.73	±1.30	2.227	>0.102	N.S

S.D = Standard deviation; F = Distribution; P = Probability value; Sig. Significant; < = Less than; > = more than

It was observed in table 6 that: There was statistically high significant difference between mean values of CRP in pleural fluid among four types of pleural effusion (p<0.001).

There was statistically high significant difference between the mean values of CRP in serum among four groups of patients in study (p<0.02).

There was no statistically significant difference between the mean values of CRP in pleural fluid to serum ratio among four groups of patients (p>0.102).

DISCUSSION

The present study was conducted to determine the level of one acute phase reactant, C-reactive protein (CRP) in exudative versus transudative pleural effusions .Forty patients who had pleural effusion due to different etiologies. Patients were selected from Chest Departments El Kasr Al-Eini in the period from May 2008 to November 2008.

Each subject signed in a special form consent that was written in simple phrase. The procedure and the aim of the work were explained to all subjects in simple. Subjects were divided into four groups: Group I: Ten patients with transudative pleural effusion; Group II: Twelve patients with tuberculous pleural effusion; Group III: Fourteen patients with malignant pleural effusion. Group IV: Four patients with bacterial cause parapneumonic pleural effusion.

Pleural effusion is a common complication of various diseases, it 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

a primary manifestation of many diseases, but most often they are observed as a secondary manifestation or complication of other disease.[13]

In the present study, Table 1 showed the gender distribution among the four groups. The incidence of malignancy in males was 71% while in females 29%. Our results are consistent with the Inas Elatter (2005), who stated that the percentage of distribution of malignancy was 64% in males in comparison to 36% in females.[9]

In our study, the incidence of tuberculous effusion was found also to be 75% in males while in females 25%, these results are going with Hopwell (2006) who stated that tuberculous effusion is more common among males.[8]

Also, in the present study the incidence of parapneumonic effusion was found to be the same percentage 50% in both males and females. While Qrtquist (2005) reported that the incidence in males is twice that in females.[19]

As regards the age distributions in different types of exudative effusion as shown in Table 2. There was statistically significant difference between the mean values for age of patients among subtypes of exudative effusion.

In our study, the mean age in tuberculous effusion was 33.33 ± 10.26 years. In addition to that 100% were tuberculin positive test ranging from 11 mm to 18 mm with lymphocytosis in pleural effusion. Barbas et al. (1991) reported that a highly positive tuberculin skin test in patients less than 40 years old.[2]

The mean age for malignancy group, in the present work, was 53 ± 14.98 years and it was in agreement with the finding of Musani and Streman (2004) in their study, they found that malignant methothelioma usually present in the fifth to seventh decade of life.[15]

As regards pleural fluid protein contents, Table 3 revealed that there were statistically high significant difference between mean values of protein in fluid, serum, and fluid to serum ratio among transudative and exudative pleural effusions. These results are in agreement with Liherman et al. (1996), who reported that fluid protein level in transudative (hepatic hydrothorax) pleural fluid is usually below 3.0 g/dl.[12]

Our results as regards protein level of fluid to serum ratio between transudative and exudative pleural effusion, there was high significant difference ($p<0.001$). These results are consistent with the finding of Light (2001), who found that if the ratio <0.5, the fluid is transudative.[14]

C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation (an acute-phase reactants). CRP is synthesized by the liver in response to factors released by fat cells (adipocytes). It is a member of the pentraxin family of proteins. It is not related to C-peptide or protein C. CRP rises up to 50,000-fold in acute inflammation, such as infection.[18] It rises above normal limits within 6 hours, and peaks at 48 hours. Its half-life is constant, and therefore its level is mainly determined by the rate of production and hence the severity of the precipitating cause. Serum amyloid A is a related acute-phase marker that responds rapidly in similar circumstance.[11]

In the present work, Table 4 revealed that there was statistically high significant difference for mean values of hs-CRP between transudative and exudative pleural fluid effusion ($p<0.003$).

Our findings are compatible with Yilmaz et al. (2000) who reported that in discrimination between exudates and transudates pleural effusions the highest sensitivity and specificity for fluid CRP were 93.7% and 76.5%, respectively. Also Alexandrakis et al. (2001) found that fluid CRP level were significantly higher in exudates than that in transudates effiision ($p<0.04$).[20,1]

While the present study found that CRP in fluid to serum ratio has no statistically significance between transudative and exudative effusion[20] suggested that CRP fluid/serum could discriminate between transudative and exudative effusion, a point which need further study on larger group of patients.

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. In pleural fluid, CRP levels have been found higher in tuberculosis and parapneumonic effusions than in other causes of pleural effusions, CRP pleural fluid level determination is useful in the diagnostic workup of lymphocytic pleural effusions. High CRP levels are very suggestive of tuberculous pleuritis, and low CRP levels make this diagnosis unlikely.[5]

As regards CRP in pleural fluid, serum and fluid to serum ratio in subtypes of exudative effusion, in our work, it was found that there were statistically significant difference of CRP level in different types of exudative pleural effusion as showed in Table 5. The mean value of CRP in tuberculous group was 3.93 mg/dl twice that found in malignant group which was l.91 mg/dl and more than that in parapneumonic group which was 1.35 mg/dl.

Also, Table 6. Revealed that there were statistically high significant difference between mean values of CRP in pleural fluid among four types of pleural effusion ($p<0.001$). Although, there was statistically high significant difference between the mean values of CRP in

serum among four groups of patients ($p<0.02$), but the difference between mean values of CRP in pleural fluid to serum ratio among four groups was statistically non-significant ($p>0.102$).

These results are going with the findings of Virdahis and Amores (1992) who concluded that fluid CRP level was twice as higher in tuberculous than in malignancy. Yilmaz et al. (2000) suggested that CRP in pleural fluid and fluid to serum ratio can be used in differential diagnosis of exudative pleural effusion subgroups such as parapneumonic, tuberculous and malignant effusion.[21,20]

Garcia E Pachon (2002) reported that the pleural CRP level were significantly higher in benign exudates than in malignant exudates.[4]

It was found in our work that fluid CRP in tuberculous effusion was statistically significant higher in comparison to that in parapneumonic effusion.

REFERENCES

1. Alexandrakis MG, Kyriakon US and Bouros U. Interleukin-6 and its relationships to acute phase proteins in serous effusion differentiation. Oncol. Rep. 2001;82:415-20.

2. Barbas CSV, Cnkier A, de-Varvalho CRR. The relationship between pleural fluid findings and the development of pleural thickening in patients with tuberculosis. Chest. 1991;100:1264-67.

3. Chen SC, W Chen, WH Thu, VH Yu, CM Shih. Role of pleural fluid C-Reactive protein concentration in discriminating uncomplicated parapneumonic pleural effusions from complicated parapneumonie effusion and empyema. Lung Journal. 2006;184.

4. Garcia E Pachon. Diagnostic value of C-reactive protein in exudative pleural effusions. European Journal of Internal Medicine. 2002;13:246-24.

5. Garcia E, Pachon E, Soler MJ, Padilla-Navas 1, Romero V, Shum C. C-reactive protein in lymphocytic pleural effusions: a diagnostic aid in tubereulous pleuritis. Respiration. 2005;724.

6. Gary T, Kinasewitz. Pleural fluid dynamic and effusion. Fishman's Pulmonary Disease and Disorders, 4th ed. 2008;2:1392-3.

7. Heffner J, Brown L, Rarbieri C. Diagnostic value of tests that discriminate between exudative and transudative pleural effusions. Primary Study Investigators. Chest. 1997;111:970-80.

8. Hopwell P. Tuberculosis and other mycobacterial diseases. Murray and Nadle's Textbook of Respiratory Medicine. Elsevier Saunders, Philadelphia. 2006;33:984-1026.

9. Inas Elatter. Lung cancer in Egypt and neighbouring countries :Magnitude and problem. UICC. 2005:21-25.

10. Kiropoulos TS, Kostikas K, Oikonoinidi S, Tsilioni I, Nikoulis U, Gerinenis A, and Gonrgonlianis KL. Acute phase markers for the differentiation of infectious and malignant pleural effusions. Respir. Med. 2007;l01:910-8.

11. Lau DC, Dhillon B, Yan H, Szmitko PE, and Vernia S. "Adipokines: molecular links between obesity and atherosclerosis". Am. J. Physiol. Heart Cire. Physiol. 2005;288:H2031-41.

12. Liherman FL, Hideniura R, Peters RL. Pathogenesis and treatment of hydrothorax complicating cirrhosis with ascites. Ann. Intern. Med. 1996;64:341-51.

13. Light RW. Diagnostic principles in pleural disease. Eur. Respir J. 1997;10:476-81.

14. Light RW. Etiology of pleural effusion, Pleural Diseases 4th Philadelphia: Lippincott Williams and Wilkins. 2001:86-95.

15. Musani AI, and Streman DH. Tumours of the mediastinum, pleura, chest wall, and diaphragm. Baum's textbook of Respiratory Medicine. 7th ed. Lippincott Williams and Wilkins; part (3). 2004:883-912.

16. Na Maskall, RIA Bhudand. BTS guide line for the investigation of a malignant pleural effusion in adult. Thorax. 2003;58:8-17.

17. Nitipatana Chierakul, Apichart Kanitsap, Angkana Chaiprasert, and Ronnachai Viriyataveekul. A simple C-reactive protein measurement for the differentiation between tuberculous and malignant pleural effusion. Respirology (Carlton, Vie.) (Respirology) 2004;9:66-9 ISSN: 1323-7799 Australia.

18. Pepys MB, Hirschfield GM. "C-reactive protein: a critical update". J. Clin. Invest.l1 2003;1:1805-12.

19. Qrtquist A, Hedlund J, Kahn M. Streptococcal pneumonia: Epidemiology, Risk factors, and clinical factors. Respir. Crit. Med. 2005;26:563-74.

20. Yilmaz TO, Yildnui Z, Turkoz Y. Use of pleural fluid C-reactive protein in diagnosis of pleural effusions. Resp. Med. 2000;94:432-5.

21. Virdahis CH, Amores AC. Metabolic and scintigraphic studied radioiodinated human C-reactive protein in healthy and disease. J. Clin. Invest. 1992;1351-57.