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USE OF C- REACTIVE PROTEIN IN PLEURAL FLUID FOR DIFFERENTIAL DIAGNOSIS OF BENIGN AND MALIGNANT EFFUSION

SUMMARY

The aim of this study was to determine the validity of pleural fluid C-reactive protein (CRP) concentrations and pleural fluid /serum CRP ratio for differentiating pleural effusion of malignant from non-malignant etiology.

Pleural fluid and serum CRP levels were obtained in 82 patients with pleural effusion, using an immunoturbidimetric method (Olympus autoanalyser). Patients were subdivided in two groups, group I (n= 41) with malignant, and group II (n=41) with non-malignant (tuberculous, inflammatory, transudative) pleural effusion.

Statistical analysis was conducted using the MannWhitney Rank sum test.

There were statistically significant differences in pleural fluid CRP values between group I (15.6 ±10.55), and group II (25.7 ±12.475), and there were significant differences between CRP pleural fluid/serum ratio in group I vs. group II (0.318 ±0.157, vs. 0.430± 0.229). In addition, there were statistically significant differences between pleural fluid CRP values in patients with parapneumonic compared to patients with tuberculous and malignant effusions. In differential diagnosis of pleural effusion, pleural fluid CRP may prove rapid and practical method of differentiating malignant from non-malignant pleural effusion.

Key words: **pleural effusion, C-reactive protein, malignant, non-malignanat**

INTRODUCTION

Pleural effusion is a common problem in clinical practice. It can be caused by several mechanisms including increased permeability of pleural membrane, increased pulmonary capillary pressure, decreased negative intrapleural pressure, decreased oncotic pressure, and obstruction of lymphatic flow (1).

Pleural effusion points to disease which can be pulmonary, pleural or extrapulmonary. One of the most common etiologies of pleural effusion is malignancy, among which lung cancer corresponds to a great number of cases. However, other infectious and other non- infectious diseases contribute to this clinical manifestation, too.

Differentiation of malignant from non-malignant pleural effusion is of great importance. Measurement of C-reactive protein (CRP) levels is clinicaly valuable screening test for inflammatory disease as a measure of response to therapy (2-4).

Acute phase response is a general response to inflammation, trigered by cytokines, released from the sites from injury or inflammation (5).

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C-reactive protein is an acute phase protein, produced in the liver. Increased production of this protein is triggered by citokones, IL 6, TNFα and IL 1, released by inflamatory cells (6). A major function of C-reactive protein is the ability to bind phosphocholine and thus recognize some foreign pathogenes 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 (3).

AIMS

The aim of the study was to investigate wheather C-reactive protein (CRP) could be clinicaly valuable for differentiating malignant from non-malignant pleural effusion.

Cytology is a standard method for diagnosis of malignant effusion, and positive pleural cytology is diagnostic of malignant pleurisy, while a positive biochemical marker values are only indicative of inflammatory process.

MATERIAL AND METHODS

We collected serum and pleural fluid samples from 82 patients, (48 man and 34 women, mean age 62,9 years) admitted to the Clinic for Lung Diseases and Clinic for Lung Surgery between March 2006 and March 2007. Blood samples were centrifuged at 1500/ 0 for 10 minutes, the pleural fluid samples were centrifuge at 2000 /o for 10 minutes to remove blood.

The levels of glucose, total protein, lactic dehydrogenase, albumin and cholesterol were measured in both sets of samples. Gram-staining and aerobic culture were performed on the pleural fluid samples. The test for mycobacterium Ziel Nilsen staining was performed after homogenisation, and the samples were cultivated in Lowenstain Jansen culture media.

CRP analysis was performed on autoanalyzer Olympus, Tokyo, Japan, using immunoturbidimetric method. CRP values are given in mg/L.

The patients were divided in two groups, group I with malignant, and group II with non-malignant pleural effusion. Effusions were considered malignat if malignant cells were found on the cytologic examination, or in the biopsy specimen.

Classification of pleural effusion into transudative or exudative is based upon Light criteria. This criteria discriminate pleural exudate on the basis of pleural fluid to serum lactate dehydrogenase ratio >0,6 , or pleural fluid to serum protein ratio >0,5 .

The diagnosis of tuberculous pleurisy was made by positive smear or culture on mycobacterium tuberculosis.

Criteria for parapneumonic effusion were: clinical, biochemical and radiological signs suspected on acute inflammation, positive culture for aerobe, positive Gram staining, presence of purulent effusion or neutrophil predominance in pleural effusion (7).

Statistical analysis was made by Mann Whitney test used to analuze the difference between groups. The level of significanse was considered as <0,05.

RESULTS

Of 82 subjects, 41 were diagnosed with malignant (group I), and 41 were diagnosed with non-malignant pleural effusion (group II). Of 41 malignant effusion, 21 subjects (51.2%) were male, and 20 (48.8%) were female. The mean age of this group was 62,8 years (range 48-80 years). Of 41 benign cases, 29 subjects (70.8%) were male, and 12 (29.2%) were female, with mean age 63.1 years (range 25-85 years). In group II, 9 (21.9%) patients had transudative, and 32 (78.1%) patients had exudative effusion. In malignant group, all patients had exudative pleural effusion. Distribution of pleural effusion etiologies are presented in *Table 1*.

Table 1. Cases of malignant and non-malignant pleural effusion

CAUSE	NUMBER	CAUSE	number
malignant	**41**	**non- malignant**	**41**
lung cancer	28	parapneumonic	13
mesotelioma	2	empyema	9
breast cancer	4	tuberculosis	9
ovary cancer	2	morbus cordis	6
endometrium	1	cyrrhosis	2
renal cancer	1	status post implantationem valvulae mitralis	1
prostate cancer	1	lupus erytematosus	1
HML	1		
carcinoma hepatis	1		

Table 2. Pleural fluid C-reactive protein levels in study group

column	n	Median	Mean±SS (mg/l)	S E	Max	Min	p
malignant	41	15.60	20.27±16,05	2.51	65.30	1.20	*
non-malignant	39	25.700	44.397±42,39*	6.788	148.900	1.500	

**data are given in mg/l, significance determinated as p<0,05 malignant vs non-malignant effusion*

Pleural fluid C-reactive protein values were significantly higher in non-malignant vs. malignant pleural effusion (Table 2.), (p<0,05). CRP values were significantly higher in parapneumonic than in malignant (p<0,001),transudative p<0,001, and in tuberculous effusions (p<0,01) (Table 3).

Differential cell counting can add some diagnostic information. Pleural lymphocytosis is common in malignant and tuberculous effusions, while neutrophilia is the sign of acute infection (9).
It is well-known that C- reactive protein values in serum is one of the most sensitive and specific

Table 3. Pleural fluid CRP values in non- malignant effusion

Column	n	Median	Mean±SD (mg/l)	S E	Max	Min	p
parapneumonic	21	65.40	68.12±43.82	9.56	148.90	12.70	*
tuberculous	9	19.50	22.28±18.15	6.05	58.50	4.10	**
transudative	9	8.300	11.15±11.53	3.84	39.40	1.50	***

*data are given in mg/l, significance determinated as p<0,05; * p<0,001 compared with malignant, ** p<0,01 compared to parapneumonic, *** p<0,001 compared to parapneumonic effusion*

The ratio of pleural fluid to serum CRP values was also significantly higher in non-malignant than in malignant group (p<0,05) (Table 4). Also, CRP pleural fluid to serum ratio was significantly higher in parapneumonic than in malignant and tuberculous group, while there were not significant differences beetwen transudative and other groups.

markers for bacterial pneumonia, and it is diagnostic as prognostic marker (10,11). There is less information about C- reacitve protein in pleural fluid. Turay et al. found that pleural fluid CRP levels >30mg/L had sensitivity of 93,7% and specifity for 76,5% for inflammatory pleural effusions (12).

Table 4. Serum/pleural fluid CRP ratio, significance determinated as p<0,05

column	n	Median	Mean±SD	SE	Max	Min	p
malignant	41	0.280	0.318±11.53	0.0245	0.870	0.1000	*
non-malignant	39	0.410	0.430±0.229	0.0366	1.020	0.0900	**
parapneumonic	21	0.48	0.51±0.25	0.054	1.02	0.09	***
tuberculous	9	0.29	0.30±0.12	0.039	0.54	0.12	
transudative	9	0.340	0.36±0.19	0.063	0.70	0.13	

** p<0,05 compared to parapneumonic, ** compared to malignant effusion , *** compared to tuberculous effusion*

DISCUSSION

Pleural effusion is often a clinical problem in medical practice, as the differential diagnosis includes a wide variety of local and systemic diseases.

Although many different diseases may cause a pleural effusion, the most common causes in the United States are congestive heart failure, pneumonia, and cancer (8). In our study, the most common cases of pleural effusion were cancer and pneumonia, which can be due to a small number of patients with congestive heart failure in our hospital.

There is a standard classification of pleural effusion into transudative an exudative effusions, based on the Light criteria. However, the etiology classification of effusions is much complex. Until now, measurements of cholesterol, bilirubin, amylase have been used, but with limited success. Vidriales at al., Turay at al. found that CRP pleural fluid levels were highly elevated in parapneumonic effusion, than in other types of effusion (12, 13). Our study show similar results. Also, the study of Turales show that pleural fluid/serum CRP ratio are much higher in parapneumonic than in malignant or tuberculous effusions. The same was with our

results. In our study, pleural fluid CRP was significantly different in malignant vs. non-malignant pleural effusion, but there is not significant difference between malignant and tuberculous effusions. On the contrary, Chierakul et al. and Garcia Patchon et al. study of CRP levels in lymphocyte pleural effusion found that CRP levels were twice as high in tuberculous than in malignant effusion, while Turay found higher CRP effusion value in malignant effusion (14,15). Retrayo et al. found that pleural fluid CRP may prove to be a rapid, practical, and accurate method to define bacterial pneumonia (16). Most of the authors who research pleural fluid CRP have found that it could be a useful marker for differentiating parapneumonic effusion from other types of effusion.

CONCLUSION

In 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. The pleural CRP level may also be helpful in discriminating between malignant from non-malignant pleural effusions.

REFERENCES

1. NA Maskell RJA. Butland. BTS guidelines for the investigation of a unilateral pleural effusion in adult. Thorax 2003; 58: 8–17.
2. Castana O, Vidriales JL, Amores Antequera C. Use of pleural fiuid C-reactive protein in laboratory diagnosis of pleural effusions. Eur J Med 1992; 1: 201-207.
3. Gubay C, Kushner I. Acute phase proteins and other systemic responses to inflammation. England Journal of Medicine 1999; 340: 448-454.
4. Diederichsen HZ, Skamling M, Diederichsen A, Grinsted P, Antonsen S. Randomised controlled trial of CRP rapid test as a guide to treatment of respiratory infections in general practice. Per Scand J Prim Health Care 2000; 141-148.
5. Melbye H. Point of care testing for C-reactive protein: A new path for Australian GPs? Australian Family Physician 2006; 35: 513-515.
6. Clyne B, Olshaker JS. The C- reactive protein. J Emerg Med 1999; 17: 1019–1025.
7. Hamm H, Light RW. Parapneumonic effusion and empyema. Eur Respir J 1997; 10: 1150–1156.
8. Light RW. Pleural effusion. N Engl J Med 2002; 346: 1971-1977.
9. Medford A, Maskell N. Pleural effusion. Postgrad Med J 2005;81:702–710.
10. Castro-Guardiola A, Armengou-Arxe A, Viejo-Rodrıguez AL, Penarroja-Matutano G, Garcia-Bragado F. Differential diagnosis between community-acquired pneumonia and nonpneumonia diseases of the chest in the emergency ward. Eur J Intern Med 2000; 11:334–339.
11. Solh AE, Pineda L, Bouquin P, Mankowski C. Determinants of short and long term functional recovery after hospitalization for community-acquired pneumonia in the elderly: role of inflammatory markers. BMC Geriatrics 2006; 6:12-15.
12. Turay YU, Yildirim Z, Turkoz Y, Biber C, Erdogan Y, Keyf AI, Ugurman F, Ayaz A, Ergun P, Harputluoglu M. Use of pleural fluid C-reactive protein in diagnosis of pleural effusions. Respir Med. 2000; 94 (5):432-435.
13. Vidriales JL, Antaquera AC. Use of C reactive protein in laboratory diagnosis of pleural effusions. Eur J Med 1992;1:201-207.
14. Chierakul N, Kanitsap A, Viriataveekul R. Simple C-reactive protein measurement for the differentiation between tuberculous and malignant pleural effusion. Respirology 2004; 9: 66–69.
15. Garcia-Patchon E, Soler MJ, Padilla-Navas I, Romero V, Shum C. C-Reactive Protein in Lymphocytic Pleural Effusions: A Diagnostic Aid in Tuberculous Pleuritis. Respiration 2005; 72: 486-489.
16. Requejo HZ, Cocoza AM. C-reactive protein in the diagnosis of community-acquired pneumonia. Braz J Infect Dis 2003; 7: 241-244.

DIJAGNOSTIČKI ZNAČAJ C-REAKTIVNOG PROTEINA U RAZLIKOVANJU MALIGNIH OD NEMALIGNIH IZLIVA

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SAŽETAK

Cilj ovog rada bio je da se ispita dijagnostički značaj određivanja C-reaktivnog proteina u izlivu, kao i odnosa CRP u izlivu i serumu, u razlikovanju malignih od nemalignih izliva.

Ispitivanjem je obuhvaćeno 82 pacijenta sa kliničkim i radiološkim znacima pleuralnog izliva, hospitalizovanih u Klinici za plućne bolesti u periodu 2006-2007. godine.

CRP je u pleuralnom izlivu i serumu određivan imunoturbidimetrijskom metodom, na autoanalajzeru Olimpus, Japan. Pacijenti su podeljeni u dve grupe, grupu I sa izlivom u sklopu maligne bolesti, i grupu II, sa nemalignom etiologijom izliva. Statistička obrada rezultata urađena je korišćenjem MannWhitney test Ran sum testa.

Postoji statistički značajna razlika u vrednostima CRPa u izlivu u grupi I i grupi II ($p<0,05$). Takođe, postoji značajna razlika u odnosu CRPa u izlivu i serumu u grupi I u odnosu na grupu II ($p<0,05$). CRP u izlivu takođe je bio statistički značajno viši kod zapaljenskih (parapneumoničnih i empijema), u odnosu na maligne ($p<0,001$), transudativne ($p<0,001$) i tuberkulozne ($p<0,01$) izlive.

Na osnovu urađenih ispitivanja, možemo zaključiti da merenje C-reaktivnog proteina u serumu predstavlja brz, dostupan test, koji može pomoći u diferenciranju malignih od nemalignih, kao i zapaljenskih od drugih tipova izliva.

Ključne reči: **pleuralni izliv, maligni, nemaligni, C-reaktivni protein**