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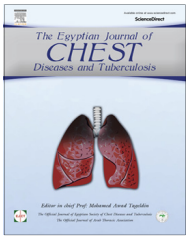

ORIGINAL ARTICLE

Role of interleukin-6 in diagnosis of pleural effusion

Mohamed A. Zamzam [a], Amal A Abd El-Aziz [a], Rabab A El Wahsh [a], Ahmed A. Sonbol [b], Shaimaa M. Abu El Nour [c,*]

[a] *Chest Department Faculty of Medicine, Menoufia University, Egypt*
[b] *Clinical pathology department Faculty of Medicine, Menoufia University, Egypt*
[c] *Elmahala chest hospital, Elgharbya Governorate, Egypt*

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KEYWORDS

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Abstract *Objectives:* To determine the level of interleukin-6 (IL-6) in both serum and pleural fluid in order to evaluate the diagnostic utility of IL-6 in differentiation between different types of pleural effusion.

Background: Pleural effusion is a relatively common clinical condition. It is often diagnostic dilemma for the physician. Interleukin-6 (IL-6) has multiple functions on various cells and tissues. It is often used as a marker for systemic activation of pro-inflammatory cytokines.

Methods: This study was conducted on 40 patients of pleural effusion, they were selected from Al-Mahalla Chest Hospital in the period between October 2012 and May 2013. All patients were subjected to detailed clinical history, thorough clinical examination, plain chest-X-ray (postero-anterior and lateral views), blood sample for: Complete blood picture (CBC), erythrocyte sedimentation rate (ESR), liver functions, renal functions and serum and pleural fluid (LDH, protein and IL-6) by ELISA.

Results: Serum and effusion IL-6 could differentiate between exudate transudate as it increased in exudate than transudate. In the present study there was higher concentration of IL-6 in the serum and pleural effusion of parapneumonic effusion than malignant and tuberculous exudative pleural effusion and higher concentration in malignant than tuberculous effusion.

Conclusion: Effusion IL-6 could be used to differentiate between exudate and transudate and serum IL-6 could be used as an alternative non invasive method for differentiation between exudates and transudate as there was a significant positive correlation between serum IL-6 and effusion IL-6.

Introduction

Pleural effusion occurs in a great variety of abnormalities. Even exhaustive diagnostic tests fail to reveal the etiology in about 20 percent of the cases [1]. Distinguishing an exudate

* Corresponding author. Tel.: +20 01228522187.
E-mail address: shoshaboalnour@gmail.com (S.M. Abu El Nour)
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from transudate is the initial step determining the cause of pleural effusion. Pleural fluid is enriched in proteins, inflammatory cells, and mediators [2]. Cytokines-producing cells and cytokines have been reported in pleural effusion from patients with malignant diseases, tuberculosis and empyema [3]. Tuberculous pleurisy (TBP) is a common cause of pleural effusion in areas with high disease prevalence, the diagnosis of TBP represents largely an immunological reaction in which a repertoire of cytokines is involved in pathogenesis. These include especially interleukin (IL) IL-22, IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), and interferon gamma (INF-γ) [4]. The pleiotropic cytokine interleukin-6 (IL-6) is a major marker of systemic response to inflammatory process and is involved in the regulation of a variety of cellular responses [5].

Aim of the study

The aim of this work is to determine the level of interleukin-6 (IL-6) in both serum and pleural fluid in order to evaluate the diagnostic utility of IL-6 in differentiation between different types of pleural effusion.

Methods

A written consent was obtained from all subjects prior to inclusion and the regional ethics committee of the Menoufia University hospital approved the study. The study was conducted in Al-Mahalla chest hospital during the period between October 2012 and May 2013. The study involved forty patients with pleural effusion; their ages ranged from 25 to 75 years. 15 were females and 25 were males.

Study subjects were divided into two groups: Group I: included 15 cases with transudative pleural effusion, and classified into Group Ia: 6 cases with transudative pleural effusions due to liver cell failure. Group Ib: 6 cases with transudative pleural effusions due to heart failure. Group Ic: 2 cases with transudative pleural effusions due to combined heart and liver cell failure. Their ages ranged from 54 to 65 years And 1 case due to renal failure. Group II: This group included 25 cases with exudative pleural effusion. This group was subdivided into: Group IIa: 4 cases with exudative tuberculous effusions, 1 male and 3 females. Group IIb: 6 cases with exudative parapneumonic pleural effusions, 5 cases were males and 1 female. Group IIc: 10 cases with exudative malignant pleural effusions, 8 cases were males and 2 females. 2 cases were with exudative collagen pleural effusions. 1 case was with exudative effusion due to pulmonary embolism. 1 case was with exudative pleural effusions due to cholecystectomy operation. 1 case was with exudative pleural effusion due to Meig's syndrome.

All subjects were subjected to: detailed clinical history, thorough clinical examination, plain chest-X-ray, blood sample for: CBC, ESR, liver functions, renal functions, serum and pleural effusion (LDH, protein and serum and IL-6).

Results

There was a statistically highly significant difference between patients with transudative and exudative pleural effusion as regards pleural fluid protein, serum LDH, pleural fluid LDH and pleural fluid IL-6 ($P \leqslant 0.001$), and a non statistically significant difference between both groups as regards serum protein ($P > 0.05$), and significant difference between the two groups as regards serum IL-6 (as shown in Table 1).

This study showed a statistically significant increase in serum and effusion LDH and highly significant increase in effusion IL-6 in patients with transudative effusion due to liver cell failure, and also showed a statistically significant increase in serum and effusion LDH in patients with transudative effusion due to heart failure in comparison with liver cell failure, while no statistically significant difference in serum and effusion LDH and effusion IL-6 in patients with transudative effusion due to combined liver cell failure and heart failure (as shown in Table 2).

This study showed that patients with parapneumonic effusion had statistically significantly higher pleural fluid LDH and IL-6 levels than non parapneumonic effusion while serum pleural fluid protein and serum LDH didn't differ between both groups (as shown in Table 3).

There was a highly significant difference between malignant and parapneumonic exudative pleural fluid as regards effusion LDH, there was a significant difference between tuberculous and parapneumonic exudative pleural effusion as regards serum IL-6, there was a significant difference between malignant and parapneumonic exudative pleural fluid as regards effusion IL-6 and there is a highly significant difference between TB and parapneumonic exudative pleural effusion as regards effusion IL-6 (as shown in Table 4).

There was a significant positive correlation between serum IL-6 and pleural fluid protein and (serum and effusion) LDH. And there was a significant positive correlation between

Table 1 Comparison between patients with transudative effusion and patients with exudative effusion as regards serum and effusion protein (g/dl), LDH (u/dl) and IL-6 (u/ml).

	Transudate (n = 15)		Exudate (n = 25)		T-test	
	Range	Mean ± SD	Range	Mean ± SD	T	P-value
Serum protein (g/dl)	5.9–8.1	6.665 ± 0.661	6–7	6.5 ± 0.4	0.8	0.4
Pleural fluid protein (g/dl)	1.2–4.1	2.3 ± 0.9	3–4.7	3.8 ± 0.45	7.03	0.000**
Serum LDH (u/dl)	87–319	199.33 ± 87.15	163–625	461.8–126.1	−76	0.000**
Pleural fluid LDH (u/dl)	109–552	318.3 ± 139.9	315–1405	884.1 ± 276.3	−7.4	0.000**
Serum IL-6 (pg/ml)	19–37	26.9 ± 5.7	14.2–190	106.6 ± 53.9	−5.7	0.03*
Pleural fluid IL-6 (pg/ml)	91–530	254.1 ± 136.4	91–1900	863.9 ± 526.2	−4.4	0.000**

* Means significant.
** Means highly significant.

Table 2 Comparison between causes of transudative pleural effusions.

		Liver cell failure ($n = 6$)	Heart failure ($n = 6$)	Liver cell failure and heart failure ($n = 2$)	ANOVA		Tukey's test		
					F	P-value	$P1$	$P2$	$P3$
Protein serum (g/dl)	Mean	6.600	6.717	6.735	0.049	0.952			
	SD	0.800	0.700	0.092					
Effusion protein (g/dl)	Mean	2.283	2.540	2.100	0.197	0.824			
	SD	0.915	0.936	1.273					
Serum LDH (u/dl)	Mean	252.333	148.833	91.000	6.176	0.016	0.05*	0.03*	0.54
	SD	83.471	49.159	5.657					
Effusion LDH (u/dl)	Mean	433.833	272.333	154.000	6.734	0.012	0.05*	0.02*	0.38
	SD	95.451	118.155	63.640					
Serum IL-6 (pg/ml)	Mean	27.833	24.000	34.500	3.586	0.063			
	SD	5.269	4.690	3.536					
Effusion IL-6 (pg/ml)	Mean	138.333	358.833	255.500	7.269	0.01	0.01**	0.36	0.44
	SD	80.421	122.048	60.104					

* Means significant.
** Means highly significant.

Table 3 Comparison between parapneumonic and non-parapneumonic exudative pleural effusion as regards (serum-effusion) protein, (serum-effusion) LDH and (serum-effusion) IL-6.

	Parapneumonic ($n = 6$)	Non parapneumonic ($n = 19$)	T-test	
	Mean ± SD	Mean ± SD	T	P-value
Serum protein (g/dl)	6.550 ± 0.383	6.521 ± 0.363	0.168	0.868
Pleural fluid protein (g/dl)	4.050 ± 0.351	3.693 ± 0.598	1.377	0.182
Serum LDH (u/dl)	492.333 ± 66.455	447.632 ± 139.705	0.749	0.461
Pleural fluid LDH (u/dl)	1155.333 ± 215.543	777.053 ± 235.841	3.488	0.002*
Serum IL-6 (pg/ml)	141.500 ± 38.014	95.563 ± 54.301	1.916	0.068
Pleural fluid IL-6 (pg/ml)	1437.667 ± 351.475	682.789 ± 436.320	3.844	0.001**

* Means significant.
** Means highly significant.

Table 4 Comparison between causes of exudative pleural effusions as regards (serum and effusion) protein, (serum and effusion) LDH and (serum and effusion) IL-6.

		ANOVA			Tukey's test	
		Mean ± SD	F	P-value	Comparison	P-value
Serum protein (gm/dl)	Malignant	6.40 ± 0.37	0.38	0.69	Malignant & TB	0.79
	TB	6.55 ± 0.42			Malignant & parapneumonic	0.73
	Parapneumonic	6.55 ± 0.38			TB & parapneumonic	1
Pleural fluid protein (gm/dl)	Malignant	3.68 ± 0.46	1.99	0.17	Malignant & TB	0.34
	TB	4.03 ± 0.31			Malignant & parapneumonic	0.21
	Parapneumonic	4.05 ± 0.35			TB & parapneumonic	1
Serum LDH (u/dl)	Malignant	470.70 ± 145.73	0.07	0.93	Malignant & TB	1
	TB	473.25 ± 44.17			Malignant & parapneumonic	0.93
	Parapneumonic	492.33 ± 66.45			TB & parapneumonic	0.96
Pleural fluid LDH (u/dl)	Malignant	809.90 ± 129.27	5.81	0.01	Malignant & TB	0.82
	TB	881.00 ± 309.84			Malignant & parapneumonic	0.01**
	Parapneumonic	1155.33 ± 215.54			TB & parapneumonic	0.11
Serum IL-6 (pg/ml)	Malignant	108.10 ± 50.48	3.57	0.05	Malignant & TB	0.24
	TB	62.55 ± 42.99			Malignant & parapneumonic	0.36
	Parapneumonic	141.50 ± 38.01			TB & parapneumonic	0.04*
Pleural fluid IL-6 (pg/ml)	Malignant	839.00 ± 472.14	7.32	0.01	Malignant & TB	0.34
	TB	493.75 ± 219.37			Malignant & parapneumonic	0.03*
	Parapneumonic	1437.67 ± 351.47			TB & parapneumonic	0.01**

* Means significant.
** Means highly significant.

Table 5 Correlation between serum and pleural effusion IL-6 and other markers.

		Serum protein	Effusion protein	Serum LDH	Effusion LDH	Serum IL-6
Serum IL-6	*R*	−0.13	0.45	0.78	0.78	
	P-value	0.42	0.003*	0000**	0000**	
Effusion IL-6	*R*	−0.11	0.43	0.67	0.77	0.87
	P-value	0.51	0.01**	.0000**	0000**	0000**

* Means significant.
** Means highly significant.

pleural fluid IL-6 and effusion protein (serum and effusion) LDH and serum IL-6 (as shown in Table 5).

Discussion

Traditionally, pleural effusions have been separated into transudative and exudative effusions [6].

In the evaluation of a pleural effusion the first step is to differentiate between transudates and exudates, if the patient has transudative effusion, no investigation needs to be directed toward the pleura and the systemic condition can be treated then the effusion will resolve. In contrast, if the patient has exudative effusion, it is important to determine the local cause that is responsible for effusion [6].

Cytokine-producing cells and cytokines have been reported in pleural effusions from patients with malignant diseases, tuberculosis, and empyema [3].

Interleukin-6 has long been regarded as a pro-inflammatory cytokine induced by lipopolysaccharide along with TNF-α and IL-1. IL-6 is often used as a marker for systemic activation of pro-inflammatory cytokines [7].

This study was designed to assess the diagnostic value of IL-6 in pleural effusion by estimation of its level in pleural effusion and serum as the cytokine interleukin-6 is a major marker of systemic response to inflammatory process and is involved in the regulation of a variety of cellular responses so used in differentiation between transudative and exudative pleural effusion [3].

In this study there were high values in exudates than transudates as regards the pleural fluid and serum LDH and IL-6 (as shown in Table 1).

These results agreed with Yokoyama et al. (1992), Ayoub et al. (2007) and Akarsu et al. (2004) who stated that IL-6 levels in pleural fluid are sensitive parameters to differentiate exudates from transudates, they found that IL-6 level increased in exudates than transudates [8–10].

On comparing between different etiologies of transudative effusion, pleural fluid due to heart failure had a significantly higher level of IL-6 than pleural fluid due to liver cell failure (as shown in Table 2).

As far as we know, no comparison between types of transudative pleural effusion as regards IL-6 level was done before but Chomeja et al. [12] estimated the concentrations of IL-6 in pleural effusion and peripheral blood from patients with tuberculosis, bronchial carcinoma and other carcinomas as well as congestive heart failure (CHF) and pneumonias. Quantitative analysis showed high concentrations of IL-6 only in parapneumonic pleural effusions. Lowest amounts were detected in CHF indicating the non-inflammatory origin of effusion.

In the present study, pleural effusion IL-6 level was higher in parapneumonic than non parapneumonic exudative effusion (as shown in Table 2).

These results matched with Akarsu et al. (2004) study that could differentiate between parapneumonic and non parapneumonic exudative effusion by estimation of effusion IL-6 level, this may be due to the continuing activation of the macrophages by the bacterial lipopolysaccharide leading to the release of cytokines (IL-1, TNF-a), which in turn promote the production of IL-6 by the stroma cells in the cases of the parapneumonic effusion [11].

In comparing the three types of exudates, in the present study there was higher concentration of IL-6 in the serum and pleural effusion of parapneumonic effusion than malignant and tuberculous exudative pleural effusion and higher concentration in malignant than tuberculous effusion (as shown in Table 3).

Xirouchaki et al. (2002) found that pleural effusion IL-6 levels were significantly higher in parapneumonic than in malignant exudates that were matched with these results [3].

On the other hand, Çigdem et al. [13], found that the tuberculous exudative pleural effusion had higher concentration of IL-6 than malignant effusion, also Xirouchaki et al. (2002), found that IL-6 level was significantly higher in tuberculous than in parapneumonic pleural fluid [3].

This difference between the results of this study and other studies may be due to large numbers of cases of parapneumonic effusion than tuberculous and malignant effusions.

In the present study there was a significant positive correlation between serum IL-6 and serum and effusion LDH and a significant positive correlation between effusion IL-6 and effusion protein, serum and effusion LDH and serum IL-6 (as shown in Table 5).

These results came in agreement with those of Yokoyama et al. (1992), who stated that pleural fluid IL-6 levels had positive correlation with serum IL-6 levels as pleural IL-6 may leak to systemic circulation to increase serum IL-6 levels [8].

Conclusion

From the present study we concluded that:

- Serum and effusion IL-6 could differentiate between exudates and transudate as it increased in exudates than transudate.
- IL-6 is an inflammatory marker and could differentiate between parapneumonic and non parapneumonic exudative effusion.

- Serum and effusion IL-6 couldn't differentiate between tuberculous and non tuberculous pleural effusion.
- Serum and effusion IL-6 couldn't differentiate between malignant and non malignant exudative pleural effusion.
- Serum IL-6 could be used as an alternative non invasive method which could differentiate between exudates and transudate as there was a significant positive correlation between serum IL-6 and effusion IL-6.

Conflict of interest

There is no conflict of interest.

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