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Cytokine Levels in Pleural Effusions of Patients under Intensive Care

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Abstract

Background: Pleural effusions develop for various reasons in patients admitted to intensive care units (ICUs). To understand why this occurs is important, yet cytokine levels in pleural effusions have rarely been measured from a cardiovascular viewpoint.

Objective: To understand the characteristics of pleural cytokines in patients admitted to the ICU.

Methods: The subjects were 43 patients with pleural effusion who were admitted to the ICU from June 2001 through March 2006. We divided the patients into transudate (n=23) and exudate (n=20) groups. We measured levels of interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-α in pleural effusions and peripheral blood and evaluated their relationships with body temperature, C-reactive protein (CRP) level, and the peripheral white blood cell (WBC) count.

Results: Levels of pleural IL-6 were significantly higher and levels of TNF-α tended to be higher in pleural effusions from the exudate than in those from the transudate group (3,350 ± 3,627 vs. 1,677 ± 1,086 pg/m and 6.6 ± 3.4 vs. 4.8 ± 2.6 pg/mL, respectively). However, in both groups levels of IL-10 in pleural effusions were similar to those in serum and levels of IL-6 were significantly higher in pleural effusion than in serum. Serum IL-6 levels correlated with inflammatory markers (CRP and body temperature), whereas cytokines in pleural effusion did not correlate with any of these markers (body temperature, CRP, and WBC).

Conclusion: Pleural levels of IL-6 were significantly higher in the exudate group than in the transudate group but did not correlate with serum levels of IL-6 or with systemic inflammatory markers. These findings suggest that pleural IL-6 levels correlate with local lung or pleural inflammation in patients admitted to the ICU.

(J Nippon Med Sch 2008; 75: 262–268)

Key words: cytokine, pleural effusion, inflammation, interleukin 6, interleukin 10, tumor necrosis factor α

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Introduction

Cytokines are endogenous mediators discharged from various types of cells which play important roles in many cell functions. Cytokines are associated with the manifestation and prolongation of systemic infectious diseases[1]. Serum levels of interleukin (IL)-6 and tumor necrosis factor (TNF)-α are intimately associated with systemic infections[2], and levels of IL-6 are also elevated in acute conditions, such as myocardial infarction, burns, and bacterial infections[3]. Serum levels of TNF-α also increase in sepsis[4]. Cytokine levels in pleural effusions are high in some infectious diseases of the lung. Akarsu et al. have found high pleural levels of IL-1β, IL-6, and IL-8 in children with empyema[5], and Porcel et al. have found elevated pleural levels of TNF-α in adults with empyema[6]. Diao and Kohanawa have shown that levels of IL-6 and IL-10 can be used to differentiate between exudates and transudate effusions in mice[7]. However, pleural effusions in patients with nonrespiratory diseases, such as acute myocardial infarction, heart failure, acute aortic dissection, and acute renal failure, have not been examined in detail. Pleural effusions can develop owing to malignancies and pneumonia and to cardiac, renal, and connective tissue diseases. Transudative effusions usually arise under noninfectious circumstances. Pleural effusions often develop in patients admitted to intensive care units (ICUs), but pleural levels of cytokines have not been investigated in such patients.

Materials and Methods

We enrolled 58 patients (mean age, 75.5 ± 9.2 years; male, 43) with pleural effusions who were admitted to the ICU from June 2001 through March 2006 because of the following conditions: cardiac diseases, 45 patients (acute coronary syndromes, 20 patients; congestive heart failure, 22 patients; myopericarditis, 2 patients; and severe arrhythmia, 1 patient); acute aortic dissection, 4 patients; infectious diseases (pneumonia and sepsis), 6 patients; malignant diseases, (lung cancer and malignant lymphoma), 2 patients; and acute renal failure, 1 patient. The patients were classified into exudate or transudate groups based on the clinical and laboratory findings of pleural effusions obtained by thoracentesis. Cut-off values for differentiating exudates from transudate were determined with the criteria of Light et al. as follows: pleural to serum protein ratio>0.5, or pleural to serum lactate dehydrogenase (LDH) ratio>0.6, or pleural LDH greater than two-thirds of the upper limit of normal serum LDH level[8]. Pleural effusion was defined as exudate when one or more of these findings were recognized. Cytokines in pleural effusions and in serum were measured with a chemiluminescence immunosorbent assay for IL-6, an enzyme-linked immunosorbent assay for IL-10, and an enzyme immunoassay for TNF-α at a clinical testing laboratory (SRL, Tokyo, Japan). Body temperature (℃), the C-reactive protein (CRP) level (mg/dL), and the peripheral white blood cell (WBC) count (number per microliter) were simultaneously measured as systemic inflammatory markers. We compared the 3 cytokines between the 2 groups of patients and investigated the correlation between cytokine concentrations and systemic infection.

Patients with unclassified pleural effusions and exceptionally high cytokine values (IL-6>20,000 pg/mL; IL-10>40.0 pg/mL; TNF-α>20.0 pg/mL) were excluded.

All numerical data are expressed as means ± standard deviation. Data were statistically analyzed using Student's *t*-test and Fisher's exact test, and a p-value of <0.05 indicated statistically significance. We obtained written, informed consent from all patients to measure cytokines at no charge and to perform therapeutic thoracentesis.

Results

Eight patients were excluded because we could not classify their pleural effusions with the criteria of Light et al. Another 7 patients were excluded because of excessively high cytokine values. Thus, 43 patients were finally included in this study. The exudate and transudate groups comprised 20 and 23 patients, respectively, and the 2 groups did not significantly differ with respect to age or sex.

Table 1 Backgrounds of patients

	Exudate group (n=20)	Transdate group (n=23)	P value
Age (years)	73.1 ± 9.0	71.4 ± 11.6	NS
Gender male/female	14/6	18/5	NS
Main diseases (cases)			
Cardiac disease	11	20	
Aortic dissection	3	0	
Infectious disease	5	2	
Malignant disease	1	1	

Table 2 Cytokines and inflammatory markers

		Exudate group (n=20)	Transdate group (n=23)	P value
pleural IL-6	(pg/mL)	3,350 ± 3,627 †	1,677 ± 1,086 †	0.0411
pleural IL-10	(pg/mL)	4.1 ± 1.9	4.0 ± 2.5	0.9362
pleural TNF-α	(pg/mL)	6.6 ± 3.4 †	4.8 ± 2.6	0.0747
serum IL-6	(pg/mL)	176 ± 205	119 ± 194	0.4174
serum IL-10	(pg/mL)	4.3 ± 4.30	3.1 ± 3.1	0.3602
serum TNF-α	(pg/mL)	4.0 ± 1.6	4.2 ± 2.2	0.8578
CRP	(mg/dL)	10.1 ± 7.8	6.5 ± 4.8	0.0740
WBC	(/μL)	9,201 ± 3,118	7,814 ± 2,843	0.1349
BT	(℃)	37.2 ± 0.4	37.0 ± 0.7	0.6054

p value, exudates versus transdates; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; WBC, white blood cell count; BT, body temperature; †, $p<0.05$ versus serum cytokine levels

Table 3 Relationship between cytokines and inflammatory markers

	CRP		WBC		BT	
	r	p value	r	p value	r	p value
Pleural IL-6	− 0.173	0.354	− 0.72	0.702	0.049	0.795
Pleural IL-10	− 0.048	0.799	− 0.195	0.296	− 0.190	0.309
Pleural TNF-α	− 0.062	0.744	− 0.277	0.132	0.042	0.276
Serum IL-6	0.432	0.014	0.131	0.485	0.412	0.021
Serum IL-10	0.166	0.376	0.106	0.572	0.14	0.457
Serum TNF-α	− 0.083	0.661	− 0.073	0.697	− 0.19	0.309

CRP, C-reactive protein; WBC, white blood cell count; BT, body temperature; IL, interleukin; TNF, tumor necrosis factor;

However, cardiac diseases were more frequent in the transudate group (**Table 1**). Although IL-6 levels were significantly higher and TNF-α levels tended to be higher in pleural effusions from the exudates group than from the transudate group (3,350 ± 3,627 vs. 1,677 ± 1,086 pg/mL; $p<0.05$ and 6.6 ± 3.4 vs. 4.8 ± 2.6 pg/mL, $p=0.07$, respectively), IL-10 concentrations were similar in the 2 groups. Levels of IL-6 were significantly higher in the pleural effusion than in serum in both groups, whereas levels of TNF-α were higher in the pleural effusion than in serum in the exudate group. Systemic inflammatory markers did not differ between the groups (**Table 2**).

Table 3 shows the relationship between cytokines and inflammatory markers. Serum IL-6 levels significantly correlated with the CRP level and body temperature, whereas levels of serum IL-10, TNF-α, and cytokines in pleural effusions did not correlate with any of these systemic inflammatory markers. **Figure 1** shows correlations between pleural and serum cytokines. Levels of IL-6, IL-10, and TNF-α in

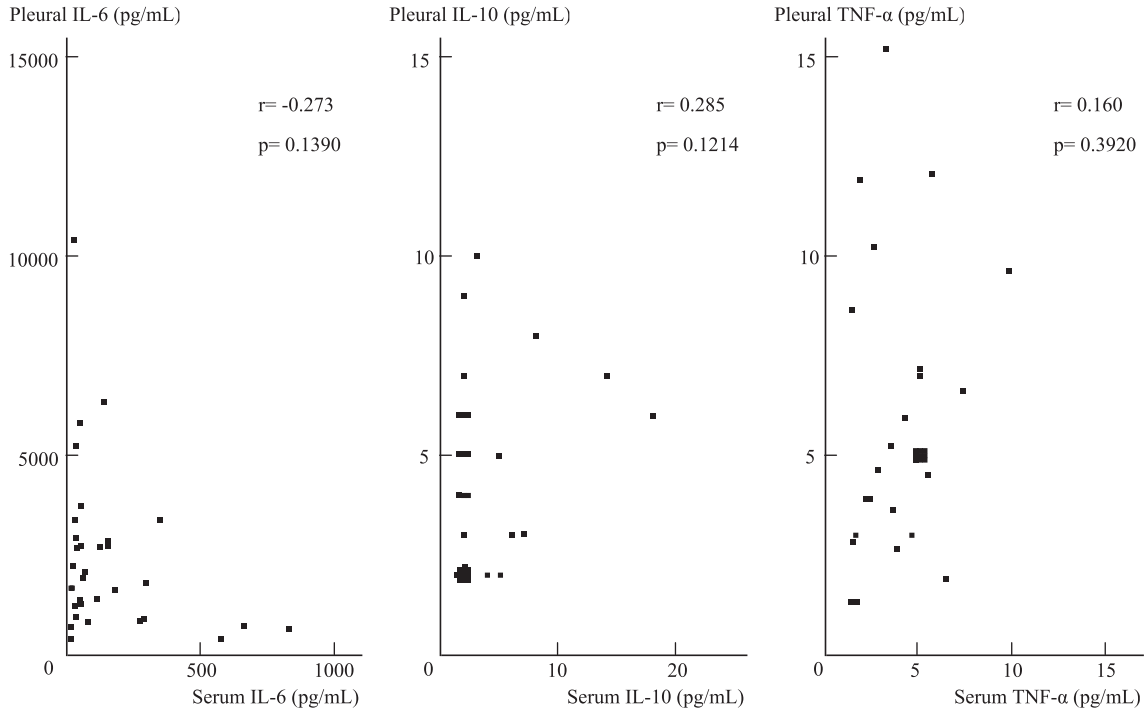

Fig. 1 Relationship between cytokines in serum and in pleural effusions.
Only serum and pleural levels of tumor necrosis factor (TNF)-α correlate.

pleural effusions did not correlated with those in serum.

Discussion

Cytokines and General Inflammation

The cytokine IL-6 mediates responses in various inflammatory processes. Serum levels of IL-6 are significantly higher in children with urinary tract or *Mycoplasma pneumoniae* infections, meningitis, or sepsis[9,10] and in adults with inflammatory conditions, such as burns and after surgery[11]. Serum levels of IL-6, TNF-α, and other cytokines are elevated in both infant and adult patients with sepsis[2,9]. Serum levels of IL-1β, IL-2, IL-6, and IL-8 have been measured in various infections[5,9]. Levels of IL-6 in the present study correlated with systemic inflammatory markers, a finding that agrees with those of previous studies[2,9–11].

Cytokines and Cardiovascular Disease

Most patients in this study had cardiovascular diseases, such as acute coronary syndrome, congestive heart failure, carditis, arrhythmias, and aortic dissection. However, the etiology of the pleural effusion was often obscured by infectious complications.

Levels of IL-6 in peripheral blood increase in patients with unstable angina[12] or acute myocardial infarction[13], and TNF-α has also been found in peripheral blood[14]. Suzuki et al. have recently reported that IL-6 levels are higher in culprit coronary arteries than in peripheral blood[15]. On the other hand, serum levels of IL-6 and TNF-α are elevated in patients with chronic[16,17] and acute decompensated[18,19] heart failure. Increased plasma levels of TNF-α and IL-6 correlate with both the severity of symptoms and the outcomes of patients with chronic heart failure[18,19]. Several neurohormonal mechanisms, including circulating catecholamines, prostaglandins, and the renin-angiotensin system, are disrupted in patients with acute decompensated heart failure, and this disruption might lead to more intense activation of mononuclear cells and increased production of proinflamatory cytokines, such as TNF-α and IL-6[20]. Thus, while many investigations have examined serum levels of and myocardial IL-6 and TNF-α, cardiovascular disease has rarely been associated with pleural cytokine levels. We found here that IL-6 levels were higher in pleural effusions

than in serum and that levels of pleural IL-6 were higher in patients with exudates than in patients with transudates. Pleural IL-6 levels might reflect local inflammation in the lung.

Cytokines and Local Inflammation

Alexandrakis et al. have reported that IL-6, IL-8, and TNF-α might be locally secreted in both benign and malignant pleural effusions at sites of active inflammation[21]. Higher serum IL-6 levels are associated with inflammatory responses to affected joints and cerebrospinal fluid in patients with rheumatoid arthritis or meningitis, respectively[22–24]. Yokoyama et al. have reported that IL-6 levels in the cerebrospinal fluid of patients with bacterial meningitis are significantly higher than in the cerebrospinal fluid of patients with aseptic meningitis or in control subjects, suggesting that understanding IL-6 values might allow sites of active inflammation to be identified[25].

On the other hand, few studies have examined cytokines in pleural effusions. We found that levels of IL-6 were significantly higher in pleural effusion than in serum and that levels of cytokines in serum, but not in pleural effusions, correlated with systemic inflammatory markers. Cytokine levels were significantly higher in exudative pleural effusions than in transudative pleural effusions. We speculate that pleural cytokine levels would be increased with local inflammation of the lung. However, because cytokine levels in pleural effusions were not affected by systemic inflammation, we conclude that they are associated with local inflammation.

IL-6 in Pleural Effusion

Akarsu et al. have found that IL-6 levels are 285-fold higher in exudative pleural effusions of infants and children than in their sera[5]. However, the correlation between serum and pleural IL-6 levels has not been examined in adults. We found that IL-6 levels in pleural effusions were significantly higher than those in serum and that serum levels and pleural levels were not correlated. Xirouchaki et al. and Yokoyama et al. have reported that IL-6 levels are significantly higher in exudative than in transudative pleural fluids[25,26]. Alexandrakis et al. have found that IL-6 levels in serum are not significantly differ between patients with exudates and those with transudates and that IL-6 levels in pleural effusions were higher in patients with tuberculous effusions than in patients with parapneumonic effusions[21]. Akarsu et al. have reported that IL-6 levels are higher in children with parapneumonic and empyematous effusions and in children with tuberculous pleural effusions[5]. Another report has shown that IL-6 levels are higher in tuberculous inflammatory exudates than in malignant exudates[27]. High pleural levels of IL-6 in infectious and tuberculous diseases might reflect accelerated humoral immunity in the pleura. Local cells, such as fibroblasts, endothelial cells, and suppressor T cells, in the pleura might accelerate the production and secretion of some cytokines. Levels of IL-6 are helpful for the diagnosis of lung diseases and reflect the extent of pleural inflammation. The same result was obtained in our study of patients in the ICU.

TNF-α in Pleural Effusions

The cytokine TNF-α plays major direct and indirect roles in host defense against invading microorganisms by killing them or by stimulating phagocytic cells, respectively[28,29]. This cytokine is located at the head of the proinflammatory cytokine cascade, and an excess of pleural TNF-α might result in pleural inflammation and destruction in patients with complicated parapneumonic effusion[29]. In addition, TNF-α can stimulate fibroblast replication and the synthesis of collagen, both of which cause pleural fibrosis[30]. Furthermore, levels of TNF-α and plasminogen activator inhibitor type I in pleural effusions increase during repeated thoracentesis in patients with malignant pleural effusions[31]. Porcel et al. have suggested that TNF-α is an excellent biochemical marker of inflammation in patients with parapneumonic effusions and have proposed that TNF-α levels would support a decision to proceed with drainage[6]. High pleural levels of TNF-α are associated with tuberculosis and empyema[32]. Barnes et al. and Kim et al. have found that TNF-α levels are higher in tuberculous pleural effusions than in nontuberculous pleural effusions[33,34],

and Xirouchaki et al. have suggested that TNF-α is elevated in all types of exudate, indicating that this proinflammatory cytokine plays a significant role in the upregulation of the immune system of the pleura[26]. These mechanisms are fundamentally similar to those involved in the high levels of IL-6 in pleural effusions.

IL-10 in Pleural Effusions

Few studies have examined pleural levels of IL-10. Chen et al. have found high concentrations of IL-10 in malignant pleural effusions and postulated that they indicate depressed immunity under these circumstances[35]. Tuberculous effusions also contain relatively higher levels of IL-10[36,37]. We found similarly high IL-10 levels in both exudative pleural effusions and in serum. IL-10 is produced by the Th2 pathway and has immunosuppressive properties, and high pleural levels of this cytokine might reflect an accelerated local cellular immune reaction via the Th2 pathway in the pleura. Furthermore, IL-10 controls the release of infectious cytokines such as TNF-α. Because IL-10 plays different physiological roles from TNF-α and IL-6, the mechanism of high IL-10 levels in pleural effusions might also differ from those of IL-6 and TNF-α.

In conclusion, IL-6 levels in pleural effusions were significantly higher than those in serum, and the two levels did not correlate. Serum, but not pleural, levels of IL-6 correlated with systemic inflammatory markers. Levels of IL-6 were significantly higher in exudative pleural effusions than in transudative pleural effusions and did not correlate with systemic inflammatory markers. We postulate that pleural IL-6 levels correlate with local lung or pleural inflammation in patients admitted to the ICU.

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(Received, April 22, 2008)
(Accepted, September 10, 2008)