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IL-8 in pleural effusion

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Interleukin-8 (IL-8) is a recently described potent chemotactic factor that may be involved in the pathogenesis of pleural effusions. To understand the actual mechanisms mediating the inflammatory response, changes in cellular components and IL-8 level in pleural fluid of different aetiologies were evaluated. Thirty-four patients (19 male, 15 female) with a mean age of 46 ± 22 years (range 16–92) were included in the study. Of these, 13 had tuberculous pleural effusion, seven had empyema/parapneumonic pleural effusion, and 14 had malignant pleural effusion (seven adenocarcinoma, three ovarian carcinoma, two lymphoma, one chronic myeloid leukaemia, and one small cell carcinoma) with positive cytology. Differential cell counts in the pleural fluid were obtained using cytocentrifuge preparations. The concentrations of IL-8 in pleural fluid were measured by the ELISA method. Interleukin-8 was detected in all 34 pleural fluid samples. The serum IL-8 level was analysed only in the empyema/parapneumonic pleural effusion group The mean IL-8 levels of tuberculous, empyema/parapneumonic, and malignant pleural effusions were 1420 ± 1049 pg ml^{-1}, 4737 ± 2297 pg ml^{-1}, and 1574 ± 1079 pg ml^{-1}, respectively. The IL-8 levels in the empyema/parapneumonic group were significantly raised over malignant and tuberculous groups ($P<0{\cdot}02$). The mean pleural fluid neutrophil counts in tuberculous, empyema/parapneumonic and malignant pleural effusions were 315 ± 575 cells mm^{-3}, 11 136 ± 12 452 cells mm^{-3}, and 635 ± 847 cells mm^{-3}, respectively ($P<0{\cdot}003$). There was a significant positive correlation between pleural IL-8 levels and neutrophil counts ($r=0{\cdot}46$, $P<0{\cdot}006$). The levels of IL-8 in paired samples of serum and pleural fluid in the empyema/parapneumonic effusion group were compared, and the concentration of IL-8 was higher in the pleural effusion than serum (means, 4737 ± 2297 pg ml^{-1} and 130·0 ± 62·5 pg ml^{-1}, respectively, $P<0{\cdot}03$). There was a significant negative correlation between IL-8 concentrations in serum and pleural fluid ($r=-0{\cdot}80$, $P<0{\cdot}03$).

This data suggests that production of IL-8 in pleural effusion may play a key role in initiation and maintenance of inflammatory reactions, especially in empyema/parapneumonic pleural effusions. It may offer the basis for introduction of novel anti-inflammatory agents in treatment.

Introduction

The movement of neutrophils from the peripheral blood into inflamed tissue is a fundamental aspect of acute inflammation. Several neutrophil chemoattractants have been characterized in recent years; the best known being the anaphylatoxin C5a, formylmethionyl peptides of bacterial origin, platelet activating factor (PAF), leukotriene B4, neutrophil activating factor-2 (NAP-2), and monocyte-derived neutrophil chemotactic factor (1–6). These stimuli have different origins and modes of formation and act via unrelated receptors suggesting that neutrophil recruitment can result from the concerted action of multiple stimuli. The effects of these chemoattractants are not restricted to neutrophils alone; monocytes and other granulocytes respond to these stimuli as well, Recent findings have demonstrated the existence of a novel neutrophil activating peptide first named NAP-1 but subsequently renamed IL-8 (7). It appears to be more selective against neutrophils, does not stimulate mononuclear phagocytes or platelets, and has only borderline effects on eosinophils and basophils. Additionally, it has been reported to be chemotactic for lymphocytes (7).

Mononuclear phagocytes, fibroblasts, epithelial cells, hepatocytes, alveolar macrophages and endothelial cells produce IL-8 in response to stimulation with inflammation-associated cytokines such as TNF, IL-1 and lipopolysaccharide (7–9). The involvement of NAP-1/IL-8 in disease is suggested by

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the demonstration of its occurrence in patients with psoriasis, arthritis, idiopathic pulmonary fibrosis, adult respiratory distress syndrome and *Pneumocystis carinii* infection (10–14).

It has been shown that IL-8 concentrations are elevated in parapneumonic and empyema fluids (15–17), there being a significant correlation with the numbers of neutrophils present (15,17). The importance of IL-8 levels in pleural effusions and serum has been poorly studied in different disease groups. This study first investigated whether IL-8 is present in human pleural effusions at physiologically significant concentrations and, if so, whether IL-8 levels correlate with the number of neutrophils. Serum IL-8 levels were determined in patients whose pleural fluid levels were high, and these levels were compared with those of the pleural fluid.

Material and Methods

Thirty-four patients (19 male, 15 female; mean age 46 ± 22 years, range 16–92 years) with pleural effusions were studied. Pleural fluid was obtained by diagnostic thoracentesis after informed consent. The effusions were first categorized as exudates using Light criteria (18). They were further categorized as either parapneumonic/empyema, tuberculous or malignant. Patients with empyema were defined by the following criteria: a positive culture for organisms, glucose concentration less than 40 mg dl^{-1} with a pleural fluid pH of less than 7·20. A parapneumonic effusion was defined as an exudative effusion associated with a pulmonary parenchymal infiltrate with a pleural fluid culture that was negative for organisms, a glucose concentration greater than 40 mg dl^{-1}, and a pleural fluid pH of more than 7·20. Tuberculous effusions were defined as those with growth on culture of pleural liquid or pleural biopsy and/or the presence of caseating granulomas on biopsy and/or acid-fast bacilli in fluid, a positive purified protein derivative (PPD) skin test, and response to anti-tuberculous therapy. A malignant pleural effusion was defined by at least one of the following criteria: malignant cells in the pleural fluid on cytologic examination, or malignancy on closed pleural biopsy. Pleural biopsies were obtained using standard techniques when tuberculosis or malignancy was suspected. A sample of fluid was placed in a haemocytometer to estimate the total number of white cells. A sample was cytocentrifuged and later stained with Wright stain for cell differential counts.

The IL-8 concentrations in pleural fluid supernatants of all patients and serums of patients with empyema/parapneumonic were measured by a sandwich-ELISA method using a commercial-kit (Amersham, U.K.). The IL-8 test kit is an enzyme immunoassay for the quantitative detection of circulating IL-8 in cell culture supernatants, human serum, amniotic or other body fluids. An anti-IL-8 monoclonal coating antibody is absorbed onto polystyrene microwells. Interleukin-8 present in the sample or standard binds to antibodies absorbed to the microwells; a horseradish peroxidase (HRP) conjugated polyclonal antibody is added and binds to the IL-8 captured by the first antibody. Unbound enzyme conjugated anti-IL-8 is removed during a wash step and the substrate solution reactive with HRP is added to the wells. A coloured product is formed in proportion to the amount of circulating IL-8 present in the sample. The reaction is terminated by the addition of acid, and absorbance measured at 450 nm. A standard curve is prepared from eight IL-8 standard dilutions in duplicate. Sample values are determined from the standard curve.

All values were expressed as the mean ± SD. Results were compared using analysis of variance. Correlation of neutrophil counts and IL-8 levels was determined by simple regression analysis (Spearman-Rank). A P value $<0{\cdot}05$ was considered to represent a significant difference.

Results

The clinical characteristics of the pleural effusions are summarized in Table 1. Thirteen patients had tuberculosis, seven patients had parapneumonic pleural effusion or empyema (three empyema, four parapneumonic), and 14 patients had malignant pleural effusion (seven adenocarcinoma, three ovarian carcinoma, two lymphoma, one chronic myeloid leukaemia, and one small cell carcinoma of the lung).

Patients with empyema/parapneumonic effusion had a marked elevation of their total cell counts, the mean being $12\,286 \pm 11\,974$ cells mm^{-3}. A large proportion of these cells were neutrophils with a few monocytes and lymphocytes. Patients with malignant pleural effusions had a large number of monocytes and lymphocytes in the pleural space. Tuberculous effusions also contained predominantly mononuclear cells (Table 1).

Interleukin-8 levels in empyema/parapneumonic effusions were significantly raised over levels in both malignant and tuberculous fluids ($P<0{\cdot}02$). In the empyema group, the pleural fluid IL-8 levels were higher than the parapneumonic group, although the number of this group was low (Table 2). In the

Table 1 Pleural fluid characteristics in different diseases

	Empyema/parapneumonic	Malignant	Tuberculosis	*P* value
No. of patients	7	14	13	
pH	7·05 ± 0·37 (6·50–7·51)	7·44 ± 0·06 (7·33–7·57)	7·35 ± 0·06 (7·30–7·41)	0·03
Total cell count (mm^{-3})	12 286 ± 11 974 (1100–28 300)	5419 ± 12 623 (200–49 000)	6301 ± 5550 (80–20 000)	n.s.
PMN cells (%)	69·4 ± 42·4 (10–100)	30·5 ± 26·9 (2–90)	8·8 ± 7·5 (0–20)	0·003
Mononuclear cells (%)	30·6 ± 42·5 (0–90)	60·0 ± 29·2 (18–100)	89·8 ± 6·7 (80–100)	0·004
Malignant cells (%)	0	24·5 ± 22·2 (2–68)	0	n.d.
Absolute PMN cell count (mm^{-3})	11 136 ± 12 452 (120–28 000)	635 ± 847 (10–2970)	315 ± 575 (8–1600)	0·003
Pleural fluid IL-8 ($pg\ ml^{-1}$)	4737 ± 2297 (210–6000)	1574 ± 1079 (70–3600)	1420 ± 1049 (185–3300)	0·02
Serum IL-8 ($pg\ ml^{-1}$)	130·0 ± 62·5 (70–210)	n.d	n.d	n.d

Data are presented as mean ± SD (range). PMN, Polymorphonuclear leucocyte; n.d., not determined; n.s., not significant.

Table 2 Pleural fluid and serum IL-8 levels in patients with empyema/parapneumonia and pleural fluid IL-8 levels in patients with tuberculosis

No. of patients	Diagnosis	Total cell count (mm^{-3})	Pleural fluid IL-8 ($pg\ ml^{-1}$)	Serum IL-8 ($pg\ ml^{-1}$)
1 MO	Parapneumonia	1100	6000	70
2 MŞ	Empyema	15 000	6000	137
3 DAŞ	Parapneumonia	9900	210	210
4 CA	Empyema	28 300	6000	70
5 AC	Parapneumonia	1200	2950	209
6 HA	Empyema	28 000	6000	72
7 YK	Parapneumonia	2500	6000	142
		12 285 ± 11 974	4737 ± 2297	130·0 ± 62·5
1 NB	Tbc (*Culture of fluid+)	80	3300	
2 FK	Tbc (†Biopsy+)	20 000	500	
3 KY	Tbc (Biopsy+)	8000	2900	
4 MA	Tbc (Culture of fluid+)	8000	640	
5 SY	Tbc (Biopsy+)	10 000	780	
6 LÖ	Tbc (Biopsy+)	2100	1280	
7 TÖ	Tbc (Culture of fluid+)	8000	1600	
8 AK	Tbc (Biopsy+, culture of pleura+)	10 000	700	
9 TB	Tbc (Biopsy+)	800	185	
10 MY	Tbc (Biopsy+)	786	600	
11 AÏ	Tbc (Biopsy+, culture of pleura+)	4700	2100	
12 SE	Tbc (Biopsy+)	1450	2900	
13 EM	Tbc (Biopsy+, culture of pleura+)	8000	975	
		6301 ± 5550	1420 ± 1049	

*BACTEC, culture of pleural fluid or pleural tissue; †Biopsy, light microscopic examination showing tuberculous granuloma.

tuberculosis group, six of thirteen patients (47%) had positive BACTEC culture, IL-8 levels in this culture positive group were not statistically different from the culture negative group ($1553 \pm 1025\ pg\ ml^{-1}$ and $1306 \pm 1138\ pg\ ml^{-1}$, respectively). The serum IL-8 levels in patients with empyema/parapneumonic were estimated and significantly lower than pleural fluid levels ($130{\cdot}0 \pm 62{\cdot}5\ pg\ ml^{-1}$ *vs.* $4737 \pm 2297\ pg\ ml^{-1}$), ($P<0{\cdot}03$), (Table 1). Furthermore, Spearman–Rank correlation test revealed a significant negative correlation between serum and pleural IL-8 levels in these patients ($r = -0{\cdot}80$, $P<0{\cdot}03$), (Fig. 1). In all groups, there was a significant positive correlation between pleural IL-8 levels and the absolute neutrophil count in the fluid ($r=0{\cdot}46$, $P<0{\cdot}006$), but not between the neutrophil percentage and IL-8 levels. However, this significant positive correlation may be due to very high neutrophil counts (Fig. 2). When the diagnostic groups were considered separately, no correlation was found between neutrophil counts and IL-8 levels in pleural fluids. There was no correlation between peripheral neutrophil counts and serum IL-8 levels.

Discussion

This study prospectively evaluated pleural fluids from 34 patients in an attempt to explain the predominance of inflammatory cell types and IL-8 levels in different disease entities. The mechanism by which neutrophil traffic is controlled in the pleural effusions is poorly understood. It was demonstrated that, in the empyema/parapneumonic group, the pleural fluid

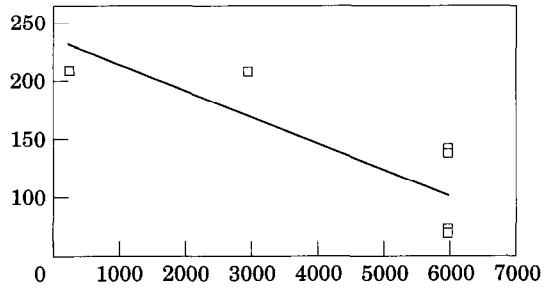

Fig 1 Correlation between serum and pleural Interleukin-8 levels in patients with empyema/parapneumonic pleural effusions ($r = -0{\cdot}80$, $P<0{\cdot}03$).

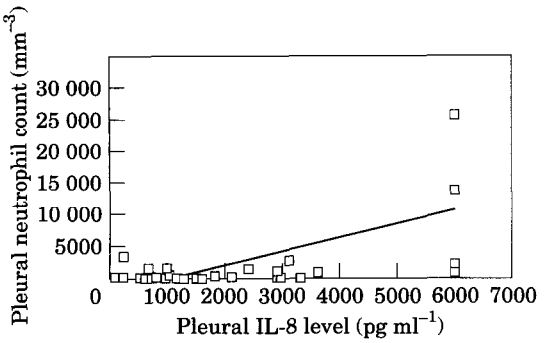

Fig 2 Correlation between Interleukin-8 levels and number of neutrophils in pleural fluids in all patients (r=0·46, P<0·06).

contained a significantly higher concentration of IL-8 than pleural fluids secondary to malignancy and tuberculosis. The IL-8 concentration correlated with the pleural fluid neutrophil count in all groups, and the level of IL-8 increased in the pleural space whilst decreasing in the serum of patients with empyema/parapneumonic pleural effusions.

Neutrophils are the major cellular component in acute inflammation and predominate in pleural fluid resulting from acute inflammation of the pleura. The increase in IL-8 concentration within inflammatory fluids was probably due to local production of the cytokine. Many cells within the pleural space have the ability to synthesize IL-8. Recently, it has been shown that human pleural mesothelial cells produce IL-8 and monocyte chemotactic peptide-1, and thus the mesothelium can sequentially regulate neutrophil and mononuclear phagocyte recruitment (19,20). Other intrapleural cells likely to produce IL-8 include macrophages and lymphocytes. Although the pleural macrophage has not yet been tested for IL-8 production, alveolar macrophages do produce IL-8 (9). Another possible cellular source is the neutrophil itself, which has been shown to produce IL-8 in response to stimuli (21). Finally, cells in the lung adjacent to the pleural space (e.g. lung fibroblasts, alveolar type II cells, intraperenchymal neutrophils) might produce IL-8 with subsequent leakage into the pleural space (22–24). Irrespective of the source of stimulus for its production, IL-8 is increased in exudative pleural effusions. Recently, Broaddus *et al.* demonstrated that empyema pleural fluid had a higher concentration of IL-8 than pleural fluids from malignant effusions, tuberculosis, and transudative effusions (17). Anthony *et al.* and Miller *et al.* reported increased IL-8 levels in empyema and parapneumonic effusions (15,16). Similarly, this study has confirmed an increase in IL-8 levels in the pleural fluid of patients with empyema/parapneumonic as compared to that in patients with malignant and tuberculous pleural fluids. In the present study, the levels of IL-8 found in patients with empyema/parapneumonic were lower than those reported by other groups, and those of malignancy/tuberculous were higher (15–17). These differences may be due to the differences in total and differential cell counts in samples. Also different ELISAs might give different results.

The concentrations of IL-8 measured in the empyema liquids were at levels consistent with physiologic activity. In *in vitro* studies of IL-8 activation of neutrophils, chemotaxis and activation are induced between 2·5 and 25 ng ml^{-1} depending on the assay (25). The IL-8 concentrations in empyema fluid are similar and, in fact, somewhat higher than those naturally occurring in undiluted human inflammatory liquids (i.e. synovial fluid) that have been assayed (11). In the present study, levels of IL-8 as high as 6000 pg ml^{-1} were found. Interleukin-8 has been shown to contribute largely to overall chemotactic activity in empyema fluids. Interestingly, in one study, addition of anti-IL-8 antibody decreased neutrophil migration by 65 ± 5% (17). In another study, removal of the IL-8 from the fluid reduced chemotactic activity between 20% and 90% (16). Antony *et al.* demonstrated that addition of anti-IL-8 antibody decreased neutrophil chemotaxis by 32·3 ± 3·28% (15). Interleukin-8 is therefore unlikely to be the only source of neutrophil chemotaxis in the pleural space. It appears, however, to be an important contributor to neutrophil chemotactic bioactivity in empyema fluid.

In the present study, there was a correlation between pleural fluid IL-8 levels and pleural fluid neutrophil counts when all patients were analysed together, but this correlation failed when results from the empyema/parapneumonic group were examined alone. A possible explanation for this difference is that neutrophil chemokines other than IL-8 are primarily responsible for the chemotactic activity for neutrophils in parapneumonic effusions, or alternatively the sample sizes may have been too small to yield a statistical difference. Anthony *et al.* found a similar negative correlation in the parapneumonic group although reporting a positive significant correlation between IL-8 levels and the total numbers of neutrophils in empyema fluids (r=0·80) (15). Broaddus *et al.* found a similar positive correlation in all groups (r=0·46) (17). Miller could find no significant difference between the mean percentage of neutrophils in pleural fluids and IL-8 levels (16).

Similarly, in the present study, no correlation was found between percentage of neutrophils and IL-8 levels.

Circulating plasma concentrations of mediators are likely to be important in the pathogenesis of inflammatory diseases. In a study by Donnelly, serum IL-8 levels were detected in patients with adult respiratory distress syndrome (ARDS) (26). No significant relation with ARDS development was found for blood IL-8 measurements. Serum levels were between 41 200 pg ml^{-1} and 0 pg ml^{-1}, with a mean of 5120 ± 2220 pg ml^{-1} (26). In another study, IL-8 levels in the sera of patients with different clinical manifestations of meningococcal disease were investigated and detected in 45% of patients with the highest incidence in septic shock. The authors reported the concentrations of IL-8 in cerebrospinal fluid to be higher than those of serum. There was, however, a significant negative association between serum IL-8 levels and the peripheral blood leucocyte counts ($r = -0{\cdot}41$, $P<0{\cdot}001$) (27). Serum IL-8 levels were determined in empyema/parapneumonic patients in this study. The findings were interesting because as pleural fluid level of IL-8 increased, serum levels dropped. Interleukin-8 appears to be compartmentalized to the pleural space in patients with neutrophilic pleural effusions. Although experimental evidence is lacking, the high levels of neutrophils encountered in the pleural fluid may contribute to the production of IL-8 although macrophages and mesothelial cells may also be sources of IL-8. To the authors' knowledge, this clinical study is the first to identify the serum IL-8 levels in patients with neutrophilic pleural effusion. However, the measurements of serum levels were only taken in the group of patients with empyema/parapneumonic effusions (seven of 34 patients). The lack of correlation between the IL-8 levels and the number of neutrophils in serum is difficult to define. This may be due to the difference of total and differential cell counts in the pleural fluid and serum.

Recently, the instillation of some drugs for pleurodesis such as tetracycline and talc have been shown to cause temporary IL-8 production and neutrophilic inflammation in the plural space (28,29). The mechanism by which IL-8 is produced in the pleural and its role in pleurodesis remains unelucidated.

The results of this study suggest that IL-8 may play a key role in recruiting neutrophils into the inflamed pleural space. Further studies of IL-8 and its role in the cytokine network in pleura and blood will be of major importance for the understanding of the pathogenesis of infectious diseases, and may ultimately have an impact on the treatment of severe infections.

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