Exhaled IL-8 in Systemic Lupus Erythematosus with and without Pulmonary Fibrosis

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Abstract The purpose of this study is to evaluate the relationship between the concentration of interleukin-8 (IL-8) in exhaled breath condensate (EBC) and bronchoalveolar lavage fluid (BALF) with the disease activity score and pulmonary function of systemic lupus erythematosus (SLE) patients with and without pulmonary fibrosis. Thirty-four SLE patients and 31 healthy controls were enrolled and evaluated using high-resolution computed tomography (HRCT), pulmonary function tests, systemic lupus activity measure (SLAM), assessing BALF and EBC. IL-8 levels in BALF and EBC samples were measured with an enzyme-immunosorbent assay kit. The mean (±SEM) IL-8 concentrations in BALF and EBC were higher in SLE patients compared to healthy controls (34.84 ± 95.0 vs. 7.65 ± 21.22 pg/ml, p < 0.001; 3.82 ± 0.52 pg/m vs. 1.7 ± 1.7 pg/ml, p < 0.001, respectively). SLE patients had increased percentage of neutrophils in BALF when compared with control group (1.00 ± 5.99 vs. 0.00 ± 0.56 %, p = 0.0003). Pulmonary fibrosis in HRCT was found in 50 % of SLE patients. The disease activity scored by SLAM was significantly higher and total lung capacity was significantly lower in SLE patients with pulmonary fibrosis (8.00 ± 3.17 vs. 6.00 ± 2.31, p = 0.01; 88.00 ± 28.29 vs. 112.00 ± 21.08 % predicted, p = 0.01, respectively). In SLE patients with pulmonary fibrosis, correlations were found between SLAM and IL-8 concentration in BALF, forced expiratory volume in 1 s and forced vital capacity (r = 0.65, p = 0.006; r = -0.53, p = 0.035; r = -0.67, p = 0.006, respectively). Our results indicate that IL-8 plays an important role in the pathogenesis of SLE. An increased concentration of IL-8 according to BALF could be considered as a useful biomarker of SLE activity and pulmonary fibrosis in SLE.

Keywords Systemic lupus erythematosus · Interleukin-8 · Exhaled breath condensate · Bronchoalveolar lavage fluid · Pulmonary fibrosis

Introduction

Cytokines play an important role in the process of organ damage in systemic lupus erythematosus (SLE). An increased level of cytokines was found in the serum, urine and cerebrospinal fluid of SLE patients and the concentration of these biomarkers was associated with the severity of the disease (Aringer and Smolen 2004; Dean et al. 2000). Interleukin-8 (IL-8) is suggested to play an important role both in the pathogenesis of SLE and pulmonary fibrosis (Keane and Strieter 2002). This is the first study estimating concentration of IL-8 in exhaled breath condensate (EBC) and bronchoalveolar lavage fluid (BALF) of...
SLE patients with and without pulmonary fibrosis with the aim of better understanding the degree to which IL-8 can be used as a prognostic factor in SLE patients. We have previously reported increased IL-6 and IL-10 concentrations in the BALF and IL-10 concentration in EBC in the same group of SLE patients (Nielepkowicz-Goździńska et al. 2013).

### Materials and Methods

The study comprised 34 patients [fulfilling the revised American College of Rheumatology criteria for the diagnosis of SLE (Hochberg 1997)] recruited from outpatient clinics and 31 healthy controls (never-smokers members of the hospital staff and medical students with normal spirometry results) matched for sex and age. In all patients high-resolution computed tomography (HRCT), spirometry, body plethysmography, diffusion capacity for carbon monoxide corrected for hemoglobin concentration (DLCOc) measurement, EBC and BALF sample collection were performed. In all healthy individuals spirometry and EBC collection were performed, while BALF fluid collection was carried out in 20. Patients were divided into two groups, one with and one without pulmonary fibrosis in HRCT chest studies. The study was carried out with the approval of the Ethics Committee of the Medical University of Lodz (RNN/146/07/KE). A written informed consent was obtained from all patients.

Sixteen patients were taking corticosteroids (prednisone: 5–20 mg/day), three of them were treated with a combination of corticosteroids and azathioprine (100–150 mg/day), and one patient was being treated with mycophenolate mofetil (1,000 mg/day). Twelve were on a maintenance dose of immunosuppressive drugs (prednisone: 5–20 mg/day, azathioprine: ≤100 mg/day). Patients with a previous history of pulmonary disorders other than SLE (asthma, chronic obstructive pulmonary disease, lung cancer, pneumonia or allergies) and with current infection were excluded from the study. The disease activity was evaluated by the systemic lupus activity measure (SLAM) (Griffiths et al. 2005) and the SLAM score median (range) 8 (3–15).

### Disease duration (years)

Disease duration (years) 8.9 ± 11.2

### SLAM score median (range)

SLAM score median (range) 8 (3–15)

### ANA ≥1:160

ANA ≥1:160 34 (100 %)

### PMP therapy

PMP therapy 16 (47 %)

### NSAID therapy

NSAID therapy 9 (26.5 %)

### Immunosuppressive (MM, A) therapy

Immunosuppressive (MM, A) therapy 4 (11.8 %)

Table 1 Demographic and clinical characteristics of SLE patients and control group

| Characteristic                | SLE patients (n = 34) | Control group (n = 31) |
|-----------------------------|----------------------|------------------------|
| Age (years)                 | 36.9 ± 11.8          | 31.2 ± 4.5             |
| Gender                      |                      |                        |
| Female                      | 31 (91.2 %)          | 27 (87.1 %)            |
| Male                        | 3 (8.8 %)            | 4 (12.9 %)             |
| Smoker                      | 4 (11.8 %)           | 0 (0 %)                |
| Disease duration (years)    | 8.9 ± 11.2           |                        |
| SLAM score median (range)   | 8 (3–15)             |                        |
| Active                      | 6 (17.7 %)           |                        |
| Inactive                    | 28 (82.3 %)          |                        |
| ANA ≥1:160                  | 34 (100 %)           |                        |
| PMP therapy                 | 16 (47 %)            |                        |
| NSAID therapy               | 9 (26.5 %)           |                        |
| Immunosuppressive (MM, A)   | 4 (11.8 %)           |                        |

A azathioprine, ANA antinuclear antibody, MM mycophenolate mofetil, MP methylprednisolone, NSAID non-steroidal anti-inflammatory drug, P prednisone, SLAM systemic lupus activity measure

The equipment (MES LUNGTEST 1000) was calibrated once daily. FVC and FEV1 were measured and the Tiffenau index was calculated.

Body plethysmography was obtained with a plethysmograph (Jaeger) and performed according to ERS standards (Wanger et al. 2005). Residual volume and total lung capacity (TLC) were measured.

DLCO diffusion capacity for carbon monoxide corrected for hemoglobin concentration was obtained with Lung Test 1000 Mes according to ATS/ERS guidelines (Macintyre et al. 2005).

EBC was collected by means of a condenser (Ecoscreen, Jaeger) and performed according to available recommendations (Horvath et al. 2005). After rinsing their mouth with distilled water, patients were asked to breathe out spontaneously for 10 min through a mouthpiece equipped with a saliva trap. A total volume of 1–3 ml of EBC samples was collected.

BALF was collected with a flexible bronchoscope (Olympus B1-IT20) according to British Thoracic Society guidelines (2001). The tip of the bronchoscope was wedged in the lingular segments and 5 aliquots of 50 ml of sterile 0.9 % NaCl solution at 37 °C were poured and recovered by gentle suction after each part. The fluid was collected, filtered through gauze and centrifuged. The pellet was suspended in phosphate buffer. Cytospins were prepared and the slides were stained with May-Grünwald Giemsa stain. The total cell count (TCC) was calculated (n × 106) under a light microscope, and the numbers of macrophages, lymphocytes, neutrophils and eosinophils were presented as percentages of the TCC.
All samples of EBC and BALF were collected in the morning (8:00 and 10:00 a.m.) in order to avoid any influence of the circadian cycle and were immediately frozen at −80 °C until assayed. The IL-8 level in BALF and EBC samples was measured with a commercially available enzyme-immunosorbent assay kit (Quantikine, R&D Systems, USA) according to the manufacturer’s protocols (the sensitivity 3.4 pg/ml for IL-8). The assay employs the quantitative sandwich immunoassay technique.

Statistical Analysis

The normality of distribution of continuous variables was tested using W test. The Student’s t test or Mann–Whitney’s U test was used for intergroup comparisons, depending on the distribution of respective variables. For comparisons of more than two groups, nonparametric analysis of variance with post hoc tests was performed using a Bonferroni-corrected Mann–Whitney’s U test for significant comparisons. Correlations were evaluated using the Pearson’s test or Spearman’s rank correlation test depending on normality of distribution. A p value of <0.05 was assumed to be statistically significant. The STATISTICA 10.0 (StatSoft, USA) package was used for analysis.

Results

SLE patients had an increased percentage of neutrophils in BALF when compared with control group (1.00 ± 5.99 vs. 0.00 ± 0.56, p = 0.0003). The mean IL-8 concentrations in BALF and EBC were higher in SLE patients compared to healthy controls (34.84 ± 95.0 vs. 7.65 ± 21.22 pg/ml, p < 0.001; 3.82 ± 0.52 pg/m vs. 1.7 ± 1.7 pg/ml, p < 0.001, respectively; Fig. 1). The concentrations of

Table 2 Correlations of SLAM in SLE patients

| Correlations                  | r value | p value |
|-------------------------------|---------|---------|
| SLAM versus lymphocytes % BALF| 0.54    | 0.001   |
| SLAM versus macrophages % BALF| −0.52   | 0.002   |
| SLAM versus neutrophils % BALF| 0.44    | 0.009   |
| SLAM versus eosinophils % BALF| −0.13   | ns (p = 0.44) |
| SLAM versus IL-8 BALF         | 0.01    | ns (p = 0.92) |
| SLAM versus IL-8 EBC          | −0.28   | ns (p = 0.10) |
| SLAM versus FEV1/FVC (%)      | −0.03   | ns (p = 0.86) |
| SLAM versus FEV1 (%pred.)     | −0.50   | 0.005   |
| SLAM versus FVC (%pred.)      | −0.57   | 0.001   |
| SLAM versus TLC (%pred.)      | −0.31   | ns (p = 0.15) |

BALF bronchoalveolar lavage fluid, EBC exhaled breath condensate, FEV1 forced expiratory volume in 1 s, FVC forced vital capacity, ns not significant, SLAM systemic lupus activity measure, TLC total lung capacity, %pred. % predicted

Table 3 HRCT positive radiological signs of pulmonary fibrosis in SLE patients

| HRCT changes                  | SLE patients |
|-------------------------------|--------------|
|                               | (n = 34)     |
| Reticular pattern             | 12 (35 %)    |
| Areas of ground glass attenuation | 2 (5.9 %)    |
| Interlobular interstitial thickening | 2 (5.9 %)    |
| Air-space nodules             | 3 (8.8 %)    |
| Honeycombing                  | 2 (5.9 %)    |
IL-8 in the EBC of all healthy persons were below the detection limit and were arbitrarily assumed to be half of the detection limit value.

In the group of SLE patients, SLAM was correlated with the percentage of neutrophils, lymphocytes and macrophages in BALF \( r = 0.44, \ p = 0.009; \ r = 0.54, \)
fibrosis are found in Table 4. The concentration of IL-8 in SLE patients with and without pulmonary fibrosis were compared with patients with normal HRCT (8.00 ± 3.17 vs. 6.00 ± 2.31; 88.00 ± 28.29 vs. 112.00 ± 21.08 % predicted, \( p = 0.01 \); \( r = -0.52 \), \( p = 0.002 \), respectively). The activity of the disease correlated negatively with FEV1 and FVC (\( r = -0.50 \), \( p = 0.005 \); \( r = -0.57 \), \( p = 0.001 \), respectively; Table 2).

Seventeen patients (50 %) were found to have pulmonary fibrosis in HRCT (Table 3). The disease activity scored by SLAM was significantly higher and TLC lower in the SLE patients with pulmonary fibrosis when compared with patients with normal HRCT (8.00 ± 3.17 vs. 6.00 ± 2.31; 88.00 ± 28.29 vs. 112.00 ± 21.08 % predicted, \( p = 0.01 \) in both). Demographic and clinical characteristics of SLE patients with and without pulmonary fibrosis are found in Table 4. The concentration of IL-8 in BALF and EBC, the spirometric results (FEV1/FVC, FEV1, FVC, TLC, DLCO) and the numbers of macrophages, lymphocytes, neutrophils and eosinophils in BALF were not significantly different in the patients with pulmonary fibrosis when compared with patients without pulmonary fibrosis (Table 5). Also there were no differences in the concentration of IL-8 in BALF when compared with patients without immunosuppressive treatment in SLE patients associated with immunosuppressive treatment (Table 6). However, among SLE patients with pulmonary fibrosis IL-8 concentration in BALF was significantly higher, FEV1 and FVC were significantly lower in patients with immunosuppressive treatment when compared with patients without immunosuppressive treatment (81.38 ± 81.23 vs. 29.61 ± 19.14, \( p < 0.05 \); 73.37 ± 18.67 vs. 101.75 ± 12.03, \( p < 0.01 \); 78.71 ± 23.76 vs. 106.00 ± 11.25, \( p < 0.05 \), respectively; Fig. 2; Table 7). SLAM was found to have negative correlations with FEV1 and FVC (\( r = -0.53 \), \( p = 0.035 \); \( r = -0.67 \), \( p = 0.006 \)) and positive correlation with IL-8 concentration in BALF (\( r = 0.65 \), \( p = 0.006 \)) in patients with pulmonary fibrosis (Fig. 3).
wide range of neutrophil functions including degranulation and respiratory burst (Knall et al. 1996). Sustained neutrophil accumulation in the alveolar space (neutrophilic alveolitis) causes lung injury and leads to interstitial fibrosis (Lynch et al. 1992; Pantelidis et al. 1997). Increased levels of IL-8 have been described in many inflammatory disorders characterized by neutrophilic infiltration, including psoriasis and rheumatoid arthritis (Biasi et al. 1998; Endo et al. 1991). The fact that IL-8 is a chemotactic cytokine which recruits the inflammatory cells to a particular location could make it a parameter of localized inflammation.

Al-Mutairi et al. (2007) report that lupus patients with pulmonary involvement have higher levels of pro-inflammatory cytokines in serum than those without pulmonary involvement. Lit et al. (2006) report a positive correlation of IL-8 plasma level with SLEDAI (systemic lupus erythematosus disease activity index in SLE patients). In the present study, the level of IL-8 was significantly higher in BALF and EBC of SLE patients. No significant differences were found in the numbers of particular BALF cells or IL-8 concentrations between patients with and without pulmonary fibrosis, despite the fact that SLAM correlates with IL-8 level in the BALF of patients with fibrotic changes in HRCT. We hypothesize that the lack of differences between patients with and without pulmonary fibrosis may be an effect of the influence of other factors like cytokines (tumor necrosis factor, IL-10), immunosuppressive therapy or the predominance of non-active SLE patients in the study. The immunosuppressive therapy is a limiting factor for the study accuracy.

An increased IL-8 level in BALF and serum of systemic sclerosis patients has been reported (Bolster et al. 1997; Furuse et al. 2003; Meloni et al. 2004). Moreover, Furuse et al. (2003) detected that elevated serum IL-8 concentrations significantly correlated with decreased percentage of DLCO in systemic sclerosis patients. They suggested that the elevation of chemokines correlates with pulmonary involvements.

The level of IL-8 mRNA in the idiopathic pulmonary fibrosis (IPF) patients correlated with the number of neutrophils in BALF and with the degree of disease severity (Carre et al. 1991). Southcott et al. (1995) suggested that the levels of IL-8 in IPF may correlate with poor prognosis.

In our study SLE patients with pulmonary fibrosis and immunosuppressive treatment had higher IL-8 concentration in BALF when compared with patients with pulmonary fibrosis and without immunosuppressive treatment. Thomas et al. (2002) observed that steroids (dexamethasone) inhibited IL-8 secretion from peripheral blood mononuclear cells, but on the other hand the inhibitory effects of steroids on IL-8 secretion were absent in infants and they developed more severe bronchiolitis. In the present study, the immunosuppressive therapy altered the results and is a limiting factor for the study. The inhibitory effects of steroids on IL-8 secretion in SLE need to be studied further.

In conclusion, to the best of our knowledge, this is the first study estimating the concentration of IL-8 in the EBC and BALF of SLE patients with and without pulmonary fibrosis. Our observations confirm the importance of IL-8
in the pathogenesis of SLE. The increased concentration of IL-8 in BALF could be considered as a marker of pulmonary fibrosis in SLE. The decision whether to start treatment is often the most difficult clinical challenge, because many patients have limited pulmonary fibrosis that will not necessarily progress. Immunosuppressive drugs could be administered to patients with an increased level of IL-8 in BALF. IL-8 in BALF may be a valuable biomarker to monitor disease activity in SLE patients with pulmonary fibrosis. IL-8 could also be used as a potential therapeutic target of pulmonary fibrosis in SLE. Further studies are necessary for the evaluation of the prognostic role of these biomarkers in the EBC and BALF of SLE patients and the inhibitory effects of steroids on IL-8 secretion in SLE patients.

| Parameter                  | With immunosuppressive treatment (n = 16) | Without immunosuppressive treatment (n = 18) | p value |
|----------------------------|------------------------------------------|---------------------------------------------|---------|
| SLAM                       | 10.75 ± 3.88                             | 7.55 ± 1.23                                 | ns      |
| Time of SLE duration (years) | 12.0 ± 6.48                              | 8.57 ± 9.50                                 | ns      |
| Lymphocytes % BALF         | 18.50 ± 12.72                            | 22.88 ± 12.23                               | ns      |
| Eosinophils % BALF         | 1.44 ± 2.55                              | 0.12 ± 0.35                                 | ns      |
| Neutrophils % BALF         | 7.37 ± 10.37                             | 3.11 ± 4.98                                 | ns      |
| Macrophages % BALF         | 77.42 ± 14.19                            | 72.22 ± 15.77                               | ns      |
| FEV1/FVC (%)               | 79.12 ± 7.18                             | 85.62 ± 8.15                                | ns      |
| FVC (%pred.)               | 78.71 ± 23.76                            | 106.00 ± 11.25                              | p < 0.05|
| FEV1 (%pred.)              | 73.37 ± 18.67                            | 101.75 ± 12.03                              | p < 0.01|
| TLC (%pred.)               | 81.71 ± 16.34                            | 97.50 ± 13.18                               | ns (p = 0.052) |
| DLCOc (%pred.)             | 98.87 ± 20.06                            | 87.77 ± 13.85                               | ns      |
| IL-8 BALF (pg/ml)          | 81.38 ± 81.23                            | 29.61 ± 19.14                               | p < 0.05|
| IL-8 EBC (pg/ml)           | 3.76 ± 0.44                              | 3.87 ± 0.38                                 | ns      |

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Conflict of interest None declared.

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