ORIGINAL ARTICLE

Exhaled cytokines in systemic lupus erythematosus with lung involvement

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KEY WORDS

bronchoalveolar lavage fluid, exhaled breath condensate, interleukin 6, interleukin 10, systemic lupus erythematosus

ABSTRACT

INTRODUCTION An inflammatory process in systemic lupus erythematosus (SLE) affects many organs including the lungs. Interleukin (IL) 6 and IL-10 are suggested to play an important role in the pathogenesis of SLE.

OBJECTIVES The aim of the study was to evaluate IL-6 and IL-10 levels in the exhaled breath condensate (EBC) and bronchoalveolar lavage fluid (BALF) of patients with and without pulmonary involvement in SLE.

PATIENTS AND METHODS The study included 34 patients with SLE and 31 healthy controls evaluated using high-resolution computed tomography, pulmonary function tests, the Systemic Lupus Activity Measure (SLAM), and IL-6 and IL-10 measurement (by an enzyme-linked immunosorbent assay) in the BALF and EBC.

RESULTS The mean IL-6 and IL-10 concentrations in the BALF and the IL-10 concentration in the EBC were higher in patients with SLE compared with healthy controls (4.03 ±8.3 vs. 0.62 ±1.2 pg/ml, $P < 0.0001$; 5.54 ±1.85 vs. 0.00 ±1.82 pg/ml, $P < 0.0001$; 8.28 ±2.7 vs. 0.00 ±1.68 pg/ml, $P < 0.0001$, respectively). The IL-10 level in the EBC correlated with SLE activity ($r = –0.40$, $P = 0.019$). The SLAM was significantly higher and the total lung capacity was significantly lower in patients with pulmonary manifestation of SLE compared with those without such complications (8.00 ±3.17 vs. 6.00 ±2.31, $P = 0.01$; 88.00 ±28.29 vs. 112 ±21.08 % predicted, $P = 0.01$; respectively). In patients with pulmonary involvement, correlations were observed between the IL-10 level in the EBC and the percentage of lymphocytes in the BALF ($r = –0.5$, $P = 0.04$).

CONCLUSIONS Our results indicate that IL-6 and IL-10 are involved in the pathogenesis of SLE. The measurement of IL-10 in the EBC may be a useful biomarker of SLE activity. It is likely that IL-10 protects against pulmonary manifestations of SLE.

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Received: December 10, 2012.
Revision accepted: February 21, 2013.
Published online: March 4, 2013.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2013; 123 (4): 141-148

INTRODUCTION Symptomatic pulmonary manifestations occur in 40% to 50% of the patients with systemic lupus erythematosus (SLE) during the course of the disease.[1] At autopsy, histological changes associated with SLE are found in almost all cases.[2] The pulmonary manifestation of lupus is an important indicator of overall prognosis.[3]

So far, few studies have been conducted to evaluate local inflammation in patients with lung involvement in SLE. The inflammatory process in the respiratory system can affect the pleura, airways, parenchyma, vasculature, and respiratory muscles.[2,4] It is well known that proinflammatory cytokines play an important role in the production of various autoantibodies in SLE. An increasing body of data shows that interleukin (IL) 6 and IL-10 are involved in the pathogenesis of lupus and related organ involvement. Therefore, we decided to analyze the concentrations of IL-6 and IL-10 in the exhaled breath condensate (EBC) and bronchoalveolar lavage fluid (BALF) of patients with SLE.

TABLE 1 Demographic and clinical characteristics of the study groups

Variables		Patients with SLE (n = 34)	Control group (n = 31)
age, y		36.9 ±11.8	31.2 ±4.5
smokers		4 (11.8)	0 (0)
sex	female	31 (91.2)	27 (87.1)
	male	3 (8.8)	4 (12.9)
disease duration, y		8.9 ±11.2	–
SLAM score, points		8 (3–15)	–
active SLE		6 (17.7)	–
inactive SLE		28 (82.3)	–
antibodies	ANA ≥1:160	34 (100)	–
	positive anti-dsDNA	4 (11.76)	–
	anti-RNP	0 (0)	–
prednisolone/methylprednisolone		16 (47)	–
NSAIDs		9 (26.5)	–
immunosuppressive therapy (azathioprine, mycophenolate mofetil)		4 (11.8)	–
fever, skin, and mucous membrane lesions		3 (8.8)	–
arthritis		15 (44.1)	–
disorders	renal	3 (8.8)	–
	cardiac	1 (2.9)	–
	neuropsychiatric	11 (32.3)	–
	gastrointerstitial	6 (17.6)	–
lymphadenopathy		0 (0)	–
anemia (Hb <12 g/dl)		6 (17.6)	–
leucopenia (WBC <3.5/10^3 µl)		7 (20.6)	–
thrombocytopenia (<150,000/10^3 µl)		3 (8.8)	–
ESR >25 mm/h		9 (26.5)	–
pulmonary changes on HRCT		17 (50)	–
fibrotic changes		12 (35)	–
areas of ground glass attenuation		2 (5.9)	–
interlobular interstitial thickening		2 (5.9)	–
air-space nodules		3 (8.8)	–
pleural effusion		1 (2.9)	–
pleural irregularities		4 (11.8)	–
honeycombing		2 (5.9)	–

Data are presented as mean ± standard deviation, number (percentage), or median (range).

Abbreviations: ANA – antinuclear antibody, anti-dsDNA – anti-double stranded DNA, anti-RNP – antibody to ribonucleoprotein, ESR – erythrocyte sedimentation rate, Hb – hemoglobin, HRCT – high-resolution computed tomography, NSAID – nonsteroidal anti-inflammatory drug, SLAM – Systemic Lupus Activity Measure, SLE – systemic lupus erythematosus, WBC – white blood cells

PATIENTS AND METHODS

The study included 34 patients fulfilling the revised American College of Rheumatology criteria for the diagnosis of SLE,[5] and 31 healthy controls matched for sex and age. Sixteen patients were taking corticosteroids (prednisone, 5–20 mg/d; methylprednisolone, 4–24 mg/d); 3 of those patients received corticosteroids in combination with azathioprine (100–150 mg/d); 1 patient received mycophenolate mofetil (1000 mg/d). Twelve patients were on a maintenance dose of immunosuppressive drugs (prednisone, ≤10 mg/d; methylprednisolone, ≤ 8 mg/d; azathioprine, ≤100 mg/d). Patients with the previous history of pulmonary disorders other than SLE and with current infection were excluded. The disease activity was evaluated by the Systemic Lupus Activity Measure (SLAM),[6] and the active disease was considered as the SLAM higher than 10. The active stage of SLE was reported in 6 patients, including 4 individuals treated with immunosuppressants (TABLE 1).

In all patients, high-resolution computed tomography (HRCT), spirometry, body plethysmography, and EBC and BALF collection were performed. Spirometry and EBC collection were performed in all healthy individuals, while BALF only in 20. Patients were divided into 2 groups based on the presence of pulmonary involvement on chest HRCT. The study was approved by the Ethics Committee of the Medical University of Lodz (RNN/146/07/KE).

TABLE 2 Concentrations of cytokines and percentage of bronchoalveolar lavage fluid cells in the study groups

Parameter		Patients with SLE (n = 34)	Control group (n = 31)	*P*
TCC BALF × 10^6 cells		32.3 ±12.5	29.2 ±9.3	NS
BALF lymphocytes, %		17.00 ±10.63	11.00 ±7.43	NS (0.086)
BALF macrophages, %		80 ±12.49	82.5 ±9.83	NS
BALF eosinophils, %		1.00 ±1.64	0.0 ±0.5	NS
BALF neutrophils, %		1.00 ±5.99	0.00 ±0.56	0.0003
IL-6, pg/ml	EBC	4.03 ±8.3	0.62 ±1.2	<0.0001
	BALF	<0.3	<0.3	–
IL-10, pg/ml	EBC	5.54 ±1.85	0.00 ±1.82	<0.0001
	BALF	8.28 ±2.7	0.00 ±1.68	<0.0001

Data are presented as mean ± standard error of the mean (median) (25th percentile; 75th percentile)

Abbreviations: BALF – bronchoalveolar lavage fluid, EBC – exhaled breath condensate, IL-6 – interleukin 6, IL-10 – interleukin 10, NS – nonsignificant, TCC – total cell count

HRCT was performed using a 64-Slice CT (GE Healthcare LightSpeed, United Kingdom) with 1.25 mm single slices, collimation at 1-centimeter intervals through the lungs, 120 kV, 265 mA, and 0.6-second scan time. The images were obtained at the window level of –700 Hounsfield units (HU) and the window width of 1500 HU, and examined independently by 2 experienced radiologists.

Spirometry was performed according to the European Respiratory Society (ERS) standards with the MES LUNGTEST 1000 model.[7] The forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were measured. The Tiffenau index (FEV_1/FVC ratio) was calculated. Body plethysmography was performed according to the ERS standards[8] with a plethysmograph (Jaeger, Germany). The residual volume (RV) and the total lung capacity were measured.

The EBC was collected using a commercial condenser (Ecoscreen, Jaeger) following the available recommendations.[9] After rinsing their mouth with distilled water, patients were asked to breathe out spontaneously for 10 minutes through a mouthpiece, and the condensate was immediately frozen.

The BALF was collected during bronchoscopy using a flexible bronchoscope (Olympus B1-IT20; Olympus Optical, Japan) according to the British Thoracic Society guidelines.[10] The tip of the bronchoscope was wedged in the lingular segments, and 5 × 50 ml aliquots 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 the gauze, and centrifuged. The pellet was suspended in a phosphate buffer. Cytospins were prepared and the slides were stained with the May-Grünwald Giemsa stain. The total cell count was calculated (n × 10^6) under the light microscope and the numbers of macrophages, lymphocytes, neutrophils, and eosinophils were presented as a percentage of the total cell count. The supernatants were immediately frozen. Bronchoscopy was always the final procedure.

All samples of the EBC and BALF were collected in the morning (8:00 and 10:00 a.m.) to avoid any effect of the circadian cycle and were immediately frozen at –80°C until assayed. IL-6 and IL-10 levels in BALF and EBC samples were measured with a commercially available enzyme-immunosorbent assay kit (Quantikine, R&D Systems, United States) according to the manufacturer's protocol. The sensitivity of the assays was 0.3 pg/ml for IL-6 and 2.3 pg/ml for IL-10.

Statistical analysis The normality of the distribution of continuous variables was tested using the Shapiro-Wilk test. The *t* test or Mann-Whitney *U* test was used for group comparisons, depending on the distribution of the respective variables. For the comparison of more than 2 groups, the nonparametric analysis of variance with post-hoc tests was performed using the Bonferroni-corrected Mann-Whitney *U* test for significant comparisons. Correlations were evaluated using the Pearson's test or Spearman's rank correlation test depending on the normality of distribution. A *P* value less than 0.05 was considered statistically significant. The STATISTICA 10.0 (StatSoft, United States) package was used for analysis.

RESULTS Among 34 patients with SLE, 17 patients were found to have pulmonary involvement on HRCT. Patients with SLE had an increased number of neutrophils in the BALF compared with the control group (1.0 ±5.99 vs. 0.00 ±0.56, $P = 0.0003$).

IL-6 was detected in all BALF samples and IL-10 in 32 BALF samples of patients with SLE. IL-6 was not detected in EBC samples, while IL-10 was detected in all EBC samples of patients with SLE. The mean IL-6 and IL-10 concentrations in the BALF and the IL-10 concentration in the EBC were higher in patients with SLE compared with controls (IL-6 BALF, 4.03 ±8.3 vs. 0.62 ±1.2 pg/ml, $P < 0.0001$; IL-10 BALF, 5.54 ±1.85 vs. 0.00 ±1.82 pg/ml, $P < 0.0001$; IL-10 EBC, 8.28 ±2.7 vs. 0.00±1.68 pg/ml, $P < 0.0001$; respectively) (TABLE 2).

The IL-10 level in the EBC was positively correlated with SLE activity ($r = –0.40$, $P = 0.019$),

TABLE 3 Statistically significant correlations of cytokines in bronchoalveolar lavage fluid and exhaled breath condensate in patients with systemic lupus erythematosus

Correlation	*r*	*P*
EBC IL-10 vs. SLAM	–0.40	0.019
EBC IL-10 vs. %BALF lymphocytes	–0.43	0.011
EBC IL-10 vs. %BALF macrophages	0.39	0.02
EBC IL-10 vs. FEV_1	0.43	0.022
EBC IL-10 vs. FVC	0.40	0.035
BALF IL-6 vs. BALF IL-10	–0.38	0.025

Abbreviations: FEV_1 – forced expiratory volume in 1 second, FVC – forced vital capacity, others – see TABLES 1 and 2

the percentage of alveolar macrophages in BALF (r = 0.39, P = 0.02), FEV_1 (r = 0.43, P = 0.022), and FVC (r = 0.40, P = 0.035). It was negatively correlated with the percentage of lymphocytes in BALF (r = –0.43, P = 0.011). The IL-10 level in BALF showed a similar tendency to correlate with SLE activity as in EBC (r = –0.29, P = 0.09) (TABLE 3). There were no correlations between IL-6 levels and the SLAM or the results of lung function tests.

Patients with pulmonary involvement The SLAM was significantly higher and the total lung capacity was significantly lower in patients with pulmonary manifestation of SLE (8.00 ±3.17 vs. 6.00 ±2.31, P = 0.01; 88.00 ±28.29 vs. 112 ±21.08 % predicted, P = 0.01; respectively) (FIGURE 1). There were no differences between patients with and without pulmonary manifestations in spirometric results and cytokine concentrations in the BALF and EBC (TABLE 4). In patients with pulmonary involvement, the IL-10 level in the EBC correlated negatively with the duration of the disease (r = –0.61, P = 0.01) and the percentage of lymphocytes in the BALF (r = –0.5, P = 0.04). It correlated positively with FEV_1 (r = 0.55, P = 0.03) and FVC (r = 0.59, P = 0.02) (FIGURE 2). The SLAM correlated negatively with FEV_1 (r = –0.53, P = 0.035) and FVC (r = –0.67, P = 0.006) (TABLE 5). In patients without pulmonary involvement, no correlations were found between the IL-10 level in the EBC and the duration of the disease, the percentage of lymphocytes in BALF, FEV_1, or FVC (data not shown). There were no differences between the levels of IL-6, IL-10 in BALF and EBC, BALF cell percentage, SLAM, FEV_1, FVC, or total lung capacity in the groups with or without immunosuppressive treatment.

DISCUSSION The pathogenesis of SLE is still only partly understood. In autoimmune diseases, the imbalance between proinflammatory and anti-inflammatory cytokines has been suggested to play an important role in its clinical and organ manifestation. Therefore, cytokines have become the subject of numerous studies to explain the pathomechanism of immune regulation in SLE.[11]

The most frequent pulmonary involvement in patients with SLE were fibrotic changes (35% of the patients; TABLE 1). The pulmonary changes related to interstitial abnormalities are observed on CT scans of 30% to 38% of the patients with SLE, even those with normal chest radiographs.[12] Our results confirmed the high prevalence of fibrotic changes in the lungs of SLE patients.

Our study has been the first to measure the concentrations of IL-6 and IL-10 in the EBC of patients with SLE. Al-Mutairi et al.[13] reported that proinflammatory cytokines (tumor necrosis factor, interferon-γ, IL-8) were more prevalent in the serum of patients with pulmonary involvement compared with those without pulmonary manifestations. However, the serum levels of IL-10 were similar in the pulmonary and non-pulmonary phenotypes.[13]

The present study revealed increased IL-10 levels in the BALF and EBC of patients with SLE. Plasma IL-10 concentrations are higher in these patients compared with healthy individuals.[14] The increase is caused particularly by excessive IL-10 production by monocytes and a subset of B cells.[15] The peripheral blood mononuclear cells of patients with lupus spontaneously produce significantly more IL-10 than those in healthy people.[16]

The disease severity correlates with elevated IL-10 concentrations.[17,18] The serum levels

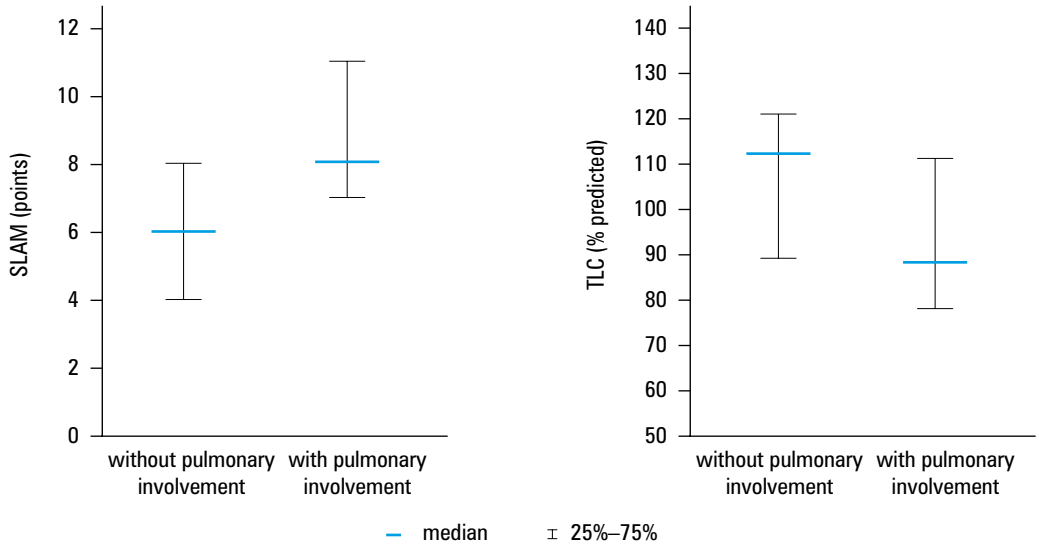

FIGURE 1 Correlations between median Systemic Lupus Activity Measure (SLAM) and total lung capacity (TLC) and pulmonary manifestations of systemic lupus erythematosus (P = 0.01, P = 0.01)

TABLE 4 Results of measurements in patients with systemic lupus erythematosus in relation to pulmonary manifestation of disease

Parameter	Pulmonary (n = 17)	Nonpulmonary (n = 17)	*P*
SLAM	8.00 ±3.17	6.00 ±2.31	0.01
disease duration, y	11.00 ±8.16	5.00 ±6.33	NS
BALF lymphocytes, %	20.82 ±12.27	16.00 ±8.27	NS
BALF eosinophils, %	0.00 ±1.94	1.00 ±1.3	NS
BALF neutrophils, %	2.0 ±8.02	1.0 ±2.02	NS
BALF macrophages, %	81 ±14.84	80 ±8.04	NS
FEV_1/FVC, %	82.37 ±8.14	85.5 ±4.94	NS
FEV_1, % predicted	90.5 ±21.09	100 ±16.59	NS
FVC, % predicted	93.26 ±22.44	106 ±15.09	NS
TLC, % predicted	88.00 ±28.29	112 ±21.08	0.01
IL-6 in BALF, pg/ml	6.7 ±9.02	5.19 ±7.89	NS
IL-6 in EBC, pg/ml	0.00 ±0.00	0.00 ±0.00	–
IL-10 in BALF, pg/ml	5.42 ±1.67	6.06 ±2.3	NS
IL-10 in EBC, pg/ml	7.44 ±2.13	8.95 ±3.06	NS

Data are presented as the mean ± standard error of the mean (median) (25th percentile; 75th percentile)

Abbreviations: see TABLES 1, 2, 3, and FIGURE 1

of IL-10 have been found to positively correlate with anti-ds DNA antibody titers and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and negatively with complement C3 levels.[19,20] However, in the present study, the IL-10 level in the EBC was found to correlate negatively with the activity of SLE, and it showed a similar tendency in the BALF. This finding could confirm that of Capper et al.[18] regarding the coexistence of groups of SLE patients with different patterns of cytokine activity. They found a group of patients with a completely different cytokine profile to that of other SLE patients; the differences could be due to varied etiologies of SLE.

Our study showed that in patients with SLE, the IL-10 level in the EBC correlated negatively with the SLAM and positively with FEV_1 and FVC. Additionally, in patients with pulmonary involvement, the IL-10 level in the EBC also correlated positively with FEV_1 and FVC, and the activity of the disease correlated negatively with FEV_1 and FVC. It is possible that IL-10 protects against pulmonary manifestations of SLE but our findings need to be confirmed.

The studies of healthy members of SLE multiplex families (families with more than 1 member with SLE) revealed higher plasma IL-10 concentrations compared with controls.[21] Treatment of SLE patients with murine anti-IL-10 monoclonal antibodies caused a clinical improvement, especially a reduction in cutaneous lesions, joint symptoms, and the SLEDAI score.[22] Increased IL-10 levels were shown to augment activation-induced apoptosis of SLE T cells and increase the burden of self-antigens. This effect is decreased by anti-IL-10 antibodies.

Both B cells and cytokines that affect B-cell survival and activation are considered the crucial factors in the pathogenesis of SLE. The effect of IL-6 is mainly proinflammatory: the activation

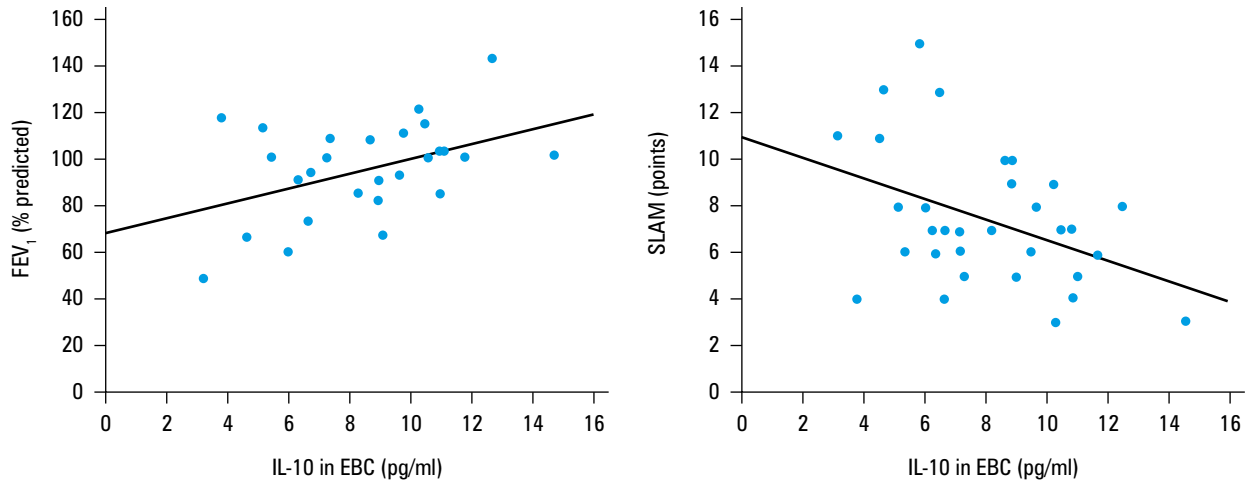

FIGURE 2 Correlations of interleukin-10 concentration in exhaled breath condensate (EBC) with forced vital capacity in 1 second (FEV_1) ($r = 0.43$, $P = 0.022$), Systemic Lupus Activity Measure (SLAM) ($r = –0.4$, $P = 0.019$) in patients with systemic lupus erythematosus

TABLE 5 Statistically significant correlations in patients with systemic lupus erythematosus with pulmonary involvement

Correlation	*r*	*P*
EBC IL-10 vs. the disease duration	–0.61	0.01
EBC IL-10 vs. %BALF lymphocytes	–0.50	0.04
EBC IL-10 vs. FEV_1	0.55	0.03
EBC IL-10 vs. FVC	0.59	0.02
BALF IL-10 vs. TLC	0.56	0.03
SLAM vs. FEV_1	–0.53	0.035
SLAM vs. FVC	–0.67	0.006

Abbreviations: see **TABLES 1**, **2**, **3**, and **FIGURE 1**

and mediation of the maturation of B cells into plasma cells, and the augmentation of immunoglobulin secretion.[23,24] IL-6 receptors are constantly present on B cells of lupus patients unlike in healthy individuals.[25]

Patients with SLE were observed to have an increased serum level of IL-6. Moreover, IL-6 concentration was associated with the severity of the disease.[26,27] The present study revealed an increased IL-6 level in the BALF of patients with SLE, and the lack of correlation between the disease activity and the IL-6 level in the BALF. Previously, the IL-6 level was reported to correlate with hematologic disease activity in patients with SLE, and high IL-6 levels were found to be present in the urine of patients with active nephritis.[28] Additionally, neuropsychiatric manifestation has been associated with an increased IL-6 concentration in the cerebrospinal fluid of SLE patients.[29] An increased plasma level of IL-6 was implicated in the development of pulmonary manifestations such as pleural effusion, lupus pneumonitis, interstitial pneumonitis, and pulmonary hypertension.[30-32] Miyata et al.[33] observed that IL-6 caused pulmonary hypertension in rats. The reports of increased IL-6 levels in the local tissues have highlighted the importance of IL-6 in the pathogenesis of local inflammation. However, our results did not reveal similar correlations.

In conclusion, our study indicates that IL-6 and IL-10 play an important role in the pathogenesis of SLE. The data suggest that the IL-10 concentration in EBC may be a useful biomarker of disease activity in SLE and may have a prognostic value. It is likely that IL-10 has a protective role against pulmonary manifestations of SLE. Further studies are necessary to evaluate the prognostic role of these biomarkers in the EBC and BALF of SLE patients.

Acknowledgments The study was funded from grant number N N402 292 336 of the Polish Ministry of Science and Higher Education.

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ARTYKUŁ ORYGINALNY

Cytokiny w wydychanym powietrzu u chorych na toczeń rumieniowaty układowy z zajęciem płuc

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SŁOWA KLUCZOWE

interleukina 6, interleukina 10, kondensat powietrza wydechowego, popłuczyny oskrzelowo-pęcherzykowe, toczeń rumieniowaty układowy

STRESZCZENIE

WPROWADZENIE Zapalenie w przebiegu tocznia rumieniowatego układowego (*systemic lupus erythematosus* – SLE) obejmuje wiele narządów, w tym płuca. Sugeruje się, że interleukiny (IL)-6 i IL-10 odgrywają ważną rolę w patogenezie SLE.

CELE Celem badania była ocena stężenia IL-6 i IL-10 w kondensacie powietrza wydechowego (*exhaled breath condensate* – EBC) i w popłuczynach oskrzelowo-pęcherzykowych (*bronchoalveolar lavage fluid* – BALF) u chorych z i bez powikłań pulmonologicznych SLE.

PACJENCI I METODY Do badania włączono 34 chorych na SLE i 31 osób zdrowych, których oceniano z wykorzystaniem tomografii komputerowej wysokiej rozdzielczości, testów czynności płuc, skali aktywności SLE (*Systemic Lupus Activity Measure* – SLAM) oraz pomiaru stężenia IL-6 i IL-10 (za pomocą testu immunoenzymatycznego) w BALF i EBC.

WYNIKI Średnie stężenie IL-6 i IL-10 w BALF i IL-10 w EBC było większe u chorych na SLE w porównaniu z osobami zdrowymi (odpowiednio: 4,03 ±8,3 *vs* 0,62 ±1,2 pg/ml, p <0,0001; 5,54 ±1,85 *vs* 0,00 ±1,82 pg/ml, p <0,0001; 8,28 ±2,7 *vs* 0,00 ±1,68 pg/ml, p <0,0001). Stężenie IL-10 w EBC korelowało z aktywnością SLE (r = –0,40; p = 0,019). Wartość SLAM była znacząco większa i całkowita pojemność płuc znacząco mniejsza u chorych z manifestacją SLE w układzie oddechowym w porównaniu z chorymi bez tych powikłań (8,00 ±3,17 *vs* 6,00 ±2,31, p = 0,01; 88,00 ±28,29 *vs* 112 ±21,08 % wn, p = 0,01). W grupie chorych na SLE z powikłaniami choroby w układzie oddechowym wykazano korelacje pomiędzy stężeniem IL-10 w EBC i odsetkiem limfocytów w BALF (r = –0,5; p = 0,04).

WNIOSKI Nasze wyniki sugerują, że IL-6 i IL-10 pełnią ważną rolę w patogenezie SLE. Pomiar stężenia IL-10 w EBC może być przydatną metodą oceny aktywności SLE. IL-10 wydaje się pełnić funkcję ochronną w procesie powstawania powikłań SLE w układzie oddechowym.

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Praca wpłynęła: 10.12.2012.
Przyjęta do druku: 21.02.2013.
Publikacja *online*: 04.03.2013.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2013; 123 (4): 141-148