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□원 저□

The Value of ICAM-1 Expression and the Soluble ICAM-1(sICAM-1) Level as a Marker of Activity in Sarcoidosis : The Relationship Between the ICAM-1 Level and the Clinical Course of the Disease

Dong Soon Kim, M.D., Sang Hoon Paik, M.D.,* Tae Sun Shim, M.D., Chae Man Lim, M.D., Sang Do Lee, M.D., Younsuck Koh, M.D., Woo Sung Kim, M.D., Won Dong Kim, M.D.

Department of Internal Medicine, Asan Medical Center-Ulsan University.
Asan Life Science Institute, Seoul, Korea.*

= Abstract =

유육종증의 활동성 지표로서의 ICAM-1

울산대학교 의과대학, 서울중앙병원, 호흡기내과, 아산생명과학연구소*

김동순, 백상훈*, 심태선, 임채만, 이상도, 고윤석, 김우성, 김원동

Background : The natural course of sarcoidosis is variable from spontaneous remission to significant morbidity or death. So the assessment of disease activity is important but no single parameter was generally accepted as a good marker. Recently several studies suggested that adhesion molecules, especially ICAM-1 can be a marker, but there are some controversies. And only few data are available about the relationship of ICAM-1 with clinical follow-up course.

Methods : We measured the expression of adhesion molecules on BAL cells by flow cytometry and the level of soluble ICAM-1(sICAM-1) in serum and BALF at the time of diagnosis in 12 patients with active disease and 7 inactive sarcoidosis(5 male, 14 female, mean age : 39.4±10.7 years, mean follpw-up : 20±15 months). Follow-up clinical course were compared with the changes in serum sICAMA-1 level and the adhesion molecule on BAL cells.

Results : In the patients with active disease, the ICAM-1 on AM(RMFI : 3.68±1.71) and sICAM-1 level in serum(582±193 ng/ml) and BAL fluid(47.8±16.5 ng/ml) were all higher than those of 7 inactive disease(RMFI : 1.89±0.75, p=0.0298, serum : 294±117 ng/ml, p=0.0049, BALF : 20.9±8.3 ng/ml). In the active sarcoidosis, ICAM-1 on AM(RMFI : 1.51±0.84) and serum sICAM-1 were decreased after the therapy(250±147 ng/ml) but no significant change was noted in inactive disease. Also we found the initial ICAM-1 on AM and serum sICAM-1 had a significant correlation with the degree of improvement in PFT after the therapy. During the follow-up, the disease relapsed in 4 patients after the discontinuation of steroid and the serum sICAM-1 level went-up again at the time of relapse.

Conclusion : Our data suggest that the serum sICAM-1 level and the ICAM-1 expression on AM can be a good marker of disease activity and also a predictor of outcome in sarcoidosis.

Introduction

Sarcoidosis is a multisystemic chronic noncaseating granulomatous disease of unknown etiology, predominatly involving intrathoracic organs [1]. The natural course of the disease is variable from spontaneous remission to continuous progression resulting in significant morbidity or death in 25~30% of the patients[2].

Corticosteroid is the most widely used drug for the sarcoidosis to prevent ocular and pulmonary fibrosis and to overcome abnormal calcium metabolism but longterm use casued serious side effects[3]. But starting the treatment too late in fibrotic phase, then no patient will be improved. So it is important to know at the time of diagnosis whether the patient's disease will remit spontaneously or deteriorate without terapy. Radiologic findings or pulmonary function test results are known to have poor correlation with the disease progression. Several different parameters, like Gallium scan, serum angiotensin converting enzyme level(SACE), ^{99m}Tc-DTPA scanning, total lymphocyte counts or T4/T8 lymohocytes ratio in BAL fluid, serum lysozyme, or soluble IL-2 receptor level were all studied but the results were often contradictory and none was proved to be a satisfactory marker[4~14]. Recently it has been known that the activation of adhesion molecules is required for the migration of the inflammatory cells to the loci of disease[15~18], and the expression of the adhesion molecules and their ligands is increased in various kinds of chronic inflammatory diseases[19~21]. Among the adhesion molecules, ICAM-1 present on endithelial cells is a ligand for beta2-integrin on neutrophils, lymphocytes and other leukocytes and it plays an important role in migration of these cells. But recently ICAM-1 is known to be present not only on endothelial cells but also on various kinds of cells including macrophages and epithelial cells[22]. Sarcoidosis is a kind of granulomatous inflammation caused by activated macrophages and lymphocytes, and the expression of ICAM-1 was reported to be increased on alveolar macrophages(AM), epthelioid cells, and giant cells in sarcoidosis[23~27]. The soluble components of ICAM-1(sICAM-1) is thought to be shed from the cell surface during binding to the ligand, its concentration in serum or extracellular fluid may reflect the degree of cell infiltration or activation[28]. There are several studies about the adhesion molecules and sICAM-1 in sarcoidosis but the results were controversial[24~27,30~34]. And there are only two reports about the change in the serum sICAM-1 level with the follow-up clinical data. The purpose of this study is to test the possibility of adhesion molecules as a marker of disease activity of sarcoidosis not only by measuring the expression of adhesion molecules on BAL cells and the serum soluble ICAM -1 level at the time of diagnosis but also comparing them with the clinical follow-up data.

Subjects and Method

1) Subjects

We studied on 19 patients who were diagnosed

as sarcoidosis by compatible clinical findings and the biopsy(transbronchial lung biopsy : 16, mediastinoscopic biopsy : 3, and skin biopsy : 3). The mean follow-up period was 20±15 months. The activity of the disease was assessed by the criteria by Boudouin et al[2]. The active disease was defined as (1) newly developed significant respiratory symptoms such as dyspnea and cough with decreased lung function at the time of diagnosis. (2) newly evolving or progressing radiological abnormality or pulmonary function during the follow-up. Twelve patients had active sarcoidosis by this criteria and 7 patients had inactive disease. All patient had lung involvement and one of the active sarcoidosis had pericardial effusion in addition to lung disease. As a control group, 9 healthy normal volunteers without respiratory symptoms or atopic diseases were studied. The demographic features and the clinical data were shown in Table 1. This study was approved by the Asan medical Center Ethics Committee.

2) Methods

At the time of diagnosis, in additon to the detailed history and physical exmination, routine pulmonary function tests including the diffusion capacity(Sensor Medics), chest radiology with HRCT, slit lamp examination, measurement of serum angiotensin converting enzyme level, serum calcium level and 24 hour urine calcium excretion, and bronchoalveolar lavage(BAL) with 50 ml aliquats 5 times, were done. BAL fluid was centrifuged at 2,000 rpm for 10 minutes and the supernatant was stored at −70℃ until the measurement. Total cell count was done with hemocytometer and the differential count was performed on the cytospin slide with Diff, Qick stain by counting 300 cells. T4 and T8 lymphocytes, and the IL-2 receptor(+) lymphocytes were measured by flow cytometry after the incubation with monoclonal antibody. Adhesion melecule expression on BAL cells were measured by flow cytometry after reacting 50 μL of 1×10^7 BAL cells with phycoerythrin-

Table 1. Demographic features of the subjects

	Normal	Sarcoidosis		
		Total	Inactive	Active
Number	9	19	7	12
Gender(M : F)	9 : 0	5 : 14	3 : 4	2 : 10
Age	36.6±10.5	39.4±10.7	38.4±8.5	39.9±12.2
Smoker	0	4	2	2
Nonsmoker	8	13	5	8
Ex-smoker	1	2	1	1
FVC(%pred)		83.9±18.5	95.6±10.4	77.2±19.0*
DLCO(%pred)		84.5±22.1	96.0±12.8	77.8±24.0*

*$p<0.05$ compared to inactive sarcoidosis

labelled monoclonal antibody for ICAM-1 (Becton-Dickins) and CD18 at 4℃ for 40 minutes. To eliminate the effect of autofluorescence of AM, we measured the mean fluorescence intensity(MFI) of AM after the incubation with idiotype control antibody and the MFI of AM reacting with anti-ICAM-1 antibody. The ICAM-1 of AM was expressed as a relative mean fluorescence intensity(RMFI), which is the ratio of MFI emitted by the bound ICAM-1 antibody to MFI of isotype control antibody[35]. Soluble ICAM -1 level in serum and BAL fluid was measured by ELISA kit(R & D System, Minneapolis, USA). For the correction of dilution effect in BAL fluid, some researchers used the ratio of solutes(ex. sICMA-1) to albumin, but it has been shown that this standardization caused more variation of the data[36]. Especially in inflamed state, that ratio to albumin is lower than in non-inflamed state, so we used measured value of sICAM-1 without correction.

3) Statistical analysis

Nonparametric method was used. Mann-Whitney U test was used for the comparison between two groups, and Spearmann rank correlation coefficient was calculated for the correlation between two parameters. All the statistical analysis were done with Macintosh Statview program.

Result

1) BAL fluid finding

The number of total cells, the number of AM, the percentage and the number of lymphocytes, and CD4/CD8 lymphocyte ratio in BAL fluid of the patients with sarcoidosis were significantly higher than those of control group(Table 2). But none of these parameters could differentiate the active sarcoidosis from inactive disease.

2) Expression of Adhesion Molecules

The ICAM-1 expression of the AM of the patients with active sarcoidosis was significantly higher(RMFI : 3.68±1.71) than not only normal

Table 2. The comparison of BAL findings between active and inactive sarcoidosis

	Normal	Sarcoidosis		
		Total	Inactive	Active
Total cell($\times 10^5$/mℓ)	0.88±0.43	2.14±0.89*	1.81±1.01	2.37±0.76
AM(%)	88.3±7.6	51.9±17.9*	57.0±21.0	49.0±46.3
AM No.($\times 10^4$/mℓ)	7.79±3.16	13.1±6.9*	9.4±3.8	14.0±7.4
Lymphocyte(%)	11.0±7.3	44.9±20.3*	38.1±21.6	48.6±19.6
Lymphocyte No.($\times 10^4$/mℓ)	1.08±0.96	10.3±8.9*	5.68±4.50	12.4±9.77
Neutrophil(%)	0.5±0.4	2.2±4.8	0.5±0.5	2.9±5.7
T4/T8	1.52±0.96	4.11±2.63*	4.03±3.56	4.15±2.56
IL-2R(+) lymphocyte(%)	8.62±8.88	8.10±5.01	8.95±7.35	7.59±3.3

* : $p<0.05$ compared to control group

control(0.94±0.17) but also inactive disease (1.89±0.75, p=0.0208). The sICAM-1 level in serum was also significantly elevated(582±193 ng/ml) in patients with active disease compared to inactive disease(294±117 ng/ml, p=0.0026) and normal control(199±38.9 ng/ml). The patients with active disease had a significantly higher sICAM-1 level in BAL fluid than normal and also incative disease(p=0.0042) (Table 3).

The ICAM-1 expression on AM had a significant correlation with sICAM-1 level in serum(p=0.004, rho=0.7) and BAL fluid(p=0.0337, rho=0.4). Also there was a significant correlation between sICAM-1 level in serum and BAL fluid(p=0.0055, rho=0.6). The ICAM-1 expression on AM correlated significantly with the total cell number and percentage and the number of AM in BAL fluid, suggesting the role of ICAM-1 in the accumulation of AM in the alveolar space. The similar correlation was noted between the sICAM-1 in BAL fluid and the cell number and the pattern(data were not shown).

3) Changes in ICAM-1 expression during the follow-up period.

During the follow-up period, the intially high serum sICAM-1 level was decreased from 582±193 ng/ml to 294±117 ng/ml in active sarcoidosis patients. In 6 patients who had repeated BAL study during the follow-up, ICAM-1 expression on AM was also reduced from 3.68±1.71 to 1.51±0.837 after the steriod treatment. In 4 patients, the disease relapsed after the discontinution of steroid treatments due to the severe side effects. The serum sICAM-1 level changed in parellel with the clinical course : it also went up at the time of relapse and in one patient, it came down again after the readministration of steroid with the relief of the symptoms(Fig. 1). Finally to assess whether ICAM-1 level can predict the patient's future outcome, we analysed the relationship between the initial ICAM-1 level and the change in PFT.

Table 3. The comparison of BAL findings between active and inactive sarcoidosis

	Normal	Sarcoidosis		
		Total	Inactive	Active
Alveolar macrophage				
ICAM-1	0.94±0.17	3.05±1.67*	1.89±0.75*	3.68±1.71**
CD 18	3.10±3.11	3.16±1.82	2.86±1.11	3.36±2.26
Lymphocyte				
ICAM-1	2.52±1.40	3.59±1.56	3.68±1.94	3.53±1.35
CD-18	6.93±6.60	22.6±13.7*	27.4±12.8*	19.8±14.4
Serum sICAM-1	199 ±38.9	480 ±218*	294 ±117	582 ±193**
BAL fluid sICAM-1	12.8±6.9	37.8±18.4*	25.2±10.3*	46.6±17.8**

* : $p<0.05$ compared to control group ** : $p<0.05$ compared to inactive sarcoidosis

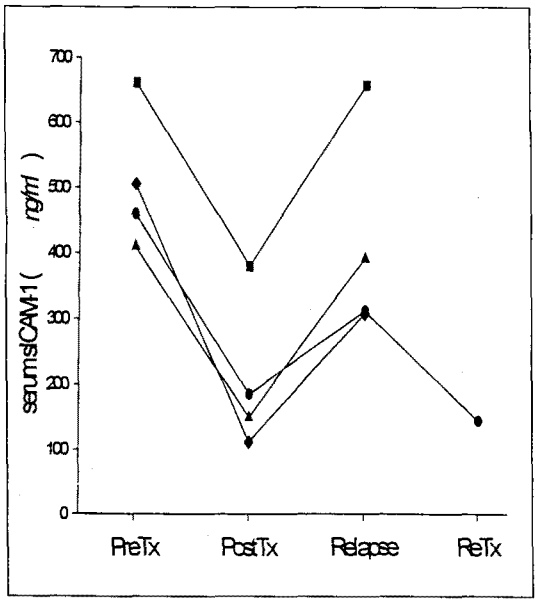

Fig. 1. The change in serum sCIAM-1 level during the course of the disease in 4 patients with sarcoidosis.

There was a significant correlation between the initial ICAM-1 expression on AM and the degree of improvement in FVC after the steroid therapy(Fig. 2). Also the initial sICAM-1 level in serum had a significant correlation with the change in FVC and DLCO($p=0.0437$, $rho=0.7$). These data suggest that the ICAM-1 expression on AM and sICAM-1 level in serum may be used as a marker of activity in sarcoidosis and also a predictor of prognosis. Serum angiotensin converting enzyme level was significaltly higher in the patients with sarcoidosis than control group but it cannot distinguish active sarcoidosis from inactive disease. Also there was no significant correlation between the serum ACE level and serum sICAM-1 level.

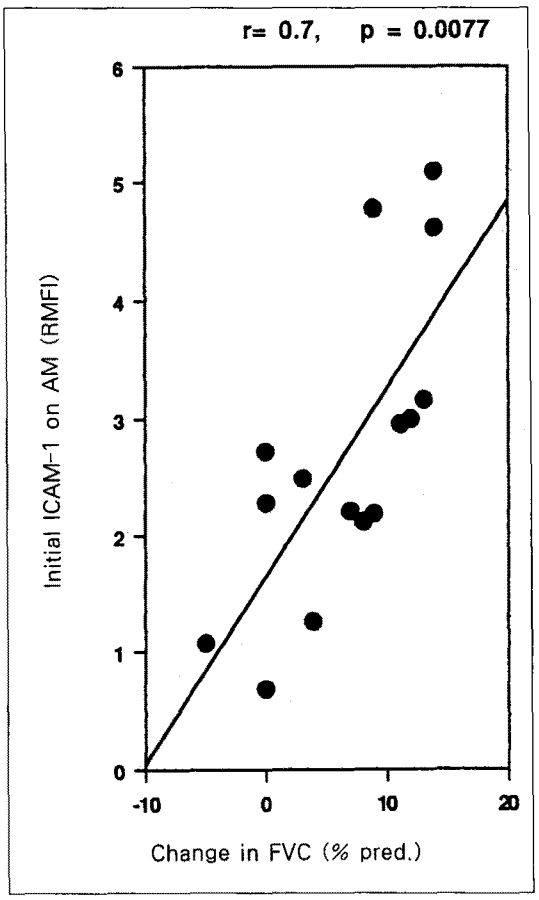

Fig. 2. Correlation between the initial ICAM-1 expression on alveolar macrophage(AM) and the degree of FVC improvement after the therapy in patients with sarcoidosis.

Discussion

Our finding of increased ICAM-1 expression on AM and increased sICAM-1 in serum and BAL fluid in active sarcoidosis than inactive disease suggests that the ICAM-1 is a marker of disease activtiy. Furthermore the change in serum

sICAM-1 level in parellel with the clinical course of the patients strongly supports this possibility. And also the initial ICAM-1 expression on AM and serum sICAM-1 levels had a significant correlation with the improvement in lung function after the therapy suggests the possibility of ICAM-1 as a predictor of the patient's outcome. The association of adhesion molecule with sarcoidosis was first reported by Melis who found increased expression of ICAM-1 and its ligand, leukocyte function associated antigen-1(LFA-1) by AM of patients with pulmonary sarcoidosis[25]. Later Van Dinther-Janssen and Shijubo reported increased expression of ICAM-1 on AM, epithelioid cells, giant cells and endothelial cells[23] in sarcoid tissue by immunohistochemistry. Also Striz, Dalhoff, and Shijubo et al observed enhanced ICAM-1 expression in BAL-AM[24~27]. In addition, Striz found the ICAM-1 on AM was correlated with the number of total cells, % of AM and IL-2R expression in BAL fluid suggesting the role of ICAM-1 in the pathogenesis of sarcoidosis[25]. Striz and Dalhoff reported that ICAM-1 on AM was increased only in clinically active sarcoidosis[26, 27] but in Stirz paper, 7 patients of 11 inactive sarcoidosis patients were on steroid therapy at the time of study in contrast to only one active sarcoidosis patient were on steroid. And our data showed decreased ICAM-1 expression on AM after the steroid. So the low level of inactive patients of striz might be due to steroid therapy. Dalhoff noted a significant correlation between ICAM-1 and spontaneous TNF-α secretion from AM[26]. But serum sICAM-1 was normal in their report. There was a some differece in the technique of measuring ICAM-1 expression. Dalhoff used semi-quantitative ELISA method[26] for the measurement of ICAM-1 expression on AM but Striz, Melis and Shijubo measured the percentage of positive cells in immunostain of BAL cells. Because ICAM-1 is constitutively expressed on normal macrophages in low level and upregulated by various stimuli like IL-1 or TNF-α, it may be sometimes difficult to evaluate the positivity on the immunostained slide, which may explain the wide range of positive cells in normal control(45%, 42.7% by Striz and Melis respectively, 10.8% by Shijubo). So we used flow cytometry which can quantitate the expression level as MFI and we eliminate the problem of autofluorescence of AM by using the ratio of MFI emited from ICAM-1 antibody to the MFI from idiotype control antibody[35]. With this technique, we confirmed the increased ICAM-1 on AM in patients with active disease compared to inactive sarcoidosis and its correlation with number of total cell, AM and lymphocytes in BAL fluid. Also we found it reduced after the steroid therapy supporting ICAM-1 expression is related to the activity of the disease. BAL is a relatively invasive test that it is difficult to repeat the test several times to evaluate the course or the response to therapy. So clinically the parameter in serum is more useful. Soluble ICAM-1 is the extracellular domain of ICAM-1 molecule and thought to be shed from the cell membrane after binding to its ligand. Therefore increased level of sICAM-1 in the body fluid indicates the enhanced ICAM-1 activity. There are several studies about the serum sICAM-1 level in sarcoidosis but the results are controversial[29~34]. Ishii, Ohmichi, and Bäumer reported increased serum sICAM-1 level in patients with sarcoido-

sis compared to normal[30~32]. In contrast Dalhoff, Shijubo and Hamblin found no significant difference in serum sICAM-1 level between sarcoidosis and normal control[24, 26, 29]. The reason of this discrepancy is not certain, but Ishii and Bäeumer studied on the patients with active disease and found the increased sICAM-1 level[30, 31]. The other researchers compared the whole sarcoidosis patients to conrol group and they did not analyze the data of the active disease separately, which may be the reason they could not find the difference. In this study we looked for the difference in serum sICAM-1 level between the patients with active sarcoidosis and inactive disease and found it significantly higher in active disease. Also we observed sICAM-1 level was reduced significantly after the steroid therapy with the symptomatic improvement and it was elevated again in four patients at the time of relapse. But in patients with inactive disease, whose clinical symptom showed no change, the serum sICAM level was stable during the follow-up, (Fig. 3). Ishii has observed the change of sICAM-1 level during the follow-up course in a small portion of their subjects[31]. And similar to our patients, Shijubo has recently observed the serum sICAM-1 level changed in accordance with the clinical course in 4 patients[34]. And they reported the serum sICAM-1 level of the patients with progressive disease was higher than the patients whose disease regressed spontaneously. All these findings together with our results strongly support that sICAM-1 is a marker of activity. In addition, our finding of significant correlation between the initial serum sICAM-1 and ICAM-1 on AM with the degree of clinical improvement supports the possibility

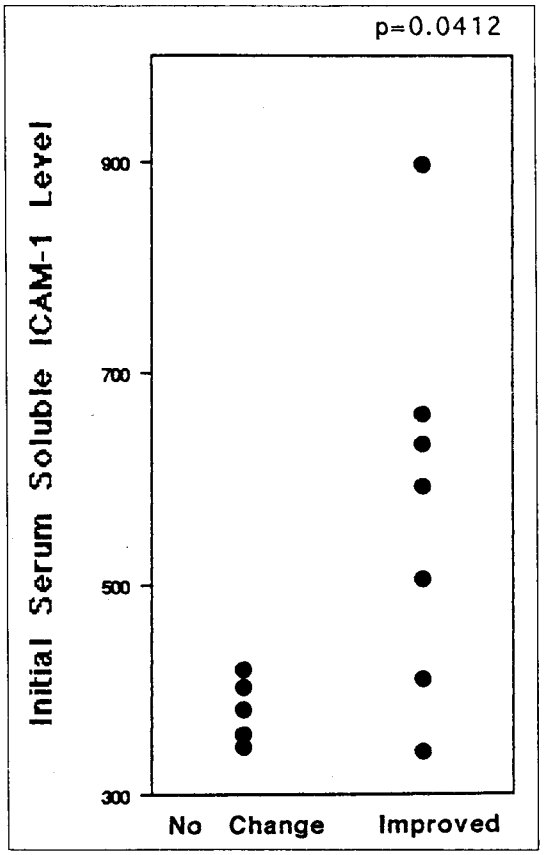

Fig. 3. The difference in the initial serum soluble ICAM-1 level between the patients whose symptom was improved and not improved.

of ICAM-1 as a predictor of clinical course. But in Shijubo's report, the disease progressed in 5 patients even though the initial sICAM level was low[34], more study in larger number of patients is needed. Shijubo and Ishii reported that sICAM-1 was elevated also in BAL fluid[24, 31] and Ishii observed a significant correlation between the serum and BAL fluid sICAM-1 level[31]. But in Shijubo's patients, no such correlation was noted [24]. We found a significant correlation between not only serum sICAM and BALF sICAM-1

level but also sICAM-1 level and ICAM-1 expression on AM. The sICAM-1 in BALF is not just simple transudation from serum but mainly produced locally, because sICAM-1/albumin ratio in BALF was much higher than that of serum(data not shown). The exact source of sICAM-1 in BALF is not certain, but its significant relationship with ICAM-1 on AM suggests that AM may be a major cellular source. But it may be from other cells, like vascular endothelial cells, epitelial cells, fibroblasts, or epithelioid cells. And the correlation between all these 3 parameters(sICAM-1 in serum, BALF, and ICAM-1 on AM) may be due to the fact that they represent one process, ie. disease activity. The number of the patients is small in our study, because sarcoidosis is still a very rare disease in Korea, even though the incidence is slowly increasing. We think our results warrent the study in larger number of patients.

국 문 초 록

연구배경 :

유육종증은 원인불명의 만성 육아종성병변으로서 전신에 다 생길수 있으나 폐문부 임파절을 위시한 흉곽내에 가장 많이 발생한다. 유육종증의 경과는 다양하여 많은 환자들이 치료없이 자연적으로 치유되나 일부 환자들에서는 병변이 계속진행하여 호흡부전이나 심지어는 사망까지도 초래하지만 어떤 환자가 계속 진행할지를 알려주는 좋은 지표는 아직도 발견되지 못하였다. 최근 염증세포들이 침윤을 위해서는 접착분자들이 활성화된다는 것이 알려짐에 따라 접착분자, 특히 ICAM-1이 이러한 유육종증이 활동성이 지표로 이용될 수 있을 가능성이 제시되었고 본 연구는 이러한 가능성을 확인하기 위하여 유육종증 환자들의 임상양상 및 그 진행경과와 폐포대식세포(AM)에서의 ICAM-1 발현도 및 혈중 가용성 ICAM-1(sICAM-1)농도 변화를 비교분석하였다.

방법 및 대상 :

조직검사로 확인된 19명의 폐유육종증환자들(남자 5명, 여자 14명, 평균 연령 : 39.4±10.7세)을 대상으로 하였고, 그 중 7명은 활동성유육종증이었고, 12명은 비활동성 환자들이었다. 진단시 BAL을 시행하여 flow cytomctry로 AM에서의 ICAM-1 발현도를 측정하고, 혈청 및 BAL액내의 sICAM-1농도를 ELISA법으로 측정하였으며, 또한 임상경과중에 혈중 sICAM-1농도도 측정하였다.

결 과 :

AM의 ICAM-1발현도는 활동성환자들에서(RMFI : 3.68±1.71)비활동성환자들보다(RMFI : 1.89±0.75, P=0.0298)유의하게 높았고, 혈청 및 BAL액내 sICAM-1농도도 활동성 유육종증에서(혈청 : 582±193 ng/ml, BALF : 47.8±16.5 ng/ml) 비활동성 환자들보다(혈청 : 294±117 ng/ml, p=0.0049, BALF : 20.9±8.3 ng/ml) 증가되어 있었다. 또한 활동성환자들의 AM의 ICAM-1발현도 및 (RMFI : 1.51±0.84) 혈중 sICAM-1 농도는 steroid치료후 유의하게 감소하였으나(250±147 ng/ml), 비활동성 환자들에서는 경과관찰중 유의한 변화는 없었다. 4명의 환자들에서는 부작용으로 steroid를 중지한 후 유육종증이 악화되었는데 이때 혈중 sICAM-1농도도 같이 증가하였으며 1명에서는 재치료후 증상호전과 함께 sICAM-1농도도 감소하였다.

결 론 :

이상의 결과로 미루어 ICAM-1, 특히 혈중 sICAM-1농도는 유육종증 활성도의 좋은 지표가 될 수 있을 것으로 사료된다.

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