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High-BAL fluid concentrations of RANTES in nonspecific interstitial pneumonia compared with usual interstitial pneumonia

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Summary Chemokines such as regulated on activation, normal T-cell expressed and secreted (RANTES), monocyte chemotactic protein (MCP)-1, monocyte inflammatory protein (MIP)\textsuperscript{a}: have been reported to play an important role in the pathogenesis of interstitial lung diseases. Among idiopathic interstitial pneumonia (IIP), nonspecific interstitial pneumonia (NSIP) has elevated percentages of lymphocytes in bronchoalveolar lavage (BAL) fluid compared with usual interstitial pneumonia (UIP). These chemokines are candidate mediators for lymphocyte attraction to the lung in NSIP. Therefore, we measured the BAL fluid levels of RANTES, MCP-1 and MIP1\textsuperscript{a} in 15 patients with idiopathic NSIP, 20 with idiopathic UIP, 22 with sarcoidosis and 12 healthy volunteers to evaluate the contribution of these chemokines using enzyme-linked immunosorbent assays. The levels of RANTES in BAL fluid were significantly higher in patients with NSIP compared with healthy volunteers (\(P<0.01\)), UIP and sarcoidosis (\(P<0.05\)). In MCP-1, the levels in BAL fluid of NSIP and UIP patients were significantly elevated compared with healthy volunteers and sarcoidosis patients (\(P<0.01\)). These results suggest that RANTES and MCP-1 in BAL fluid may play an important role in inflammatory cell recruitment to the lung in idiopathic NSIP as well as other interstitial lung diseases.

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Introduction

The classification of idiopathic interstitial pneumonia (IIP) includes seven clinico-radiologic-pathologic entities. Usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) are the two largest subsets of IIP.\textsuperscript{1-3} NSIP is distinguished from UIP by a temporal uniformity of interstitial inflammation and/or fibrosis on histology.\textsuperscript{1-3} The distinction between NSIP and UIP is important for clinical decision-making because the prognosis is generally good and the response to corticosteroids and immunosuppressants is also good in patients with NSIP compared with UIP.\textsuperscript{1-3} It is well known that NSIP has a relative lymphocytosis with a predominance of CD8\textsuperscript{+} cells in BAL fluid when compared with UIP.\textsuperscript{4,6} An association between the lymphocytosis and the levels of IL-6 in BAL fluid of patients with NSIP has also been reported.\textsuperscript{5} These suggest that NSIP has a pathogenesis different from UIP, but this still remains unclear.
It is well known that C–C chemokines such as monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP1-α), and regulated upon activation, normal T-cell expressed and secreted (RANTES) are closely related to the expression of adhesion molecules and the migration of inflammatory cells into the lung. These chemokines have been reported to be important factors in interstitial lung diseases.7–16 RANTES has been reported to be a chemotactic factor of certain lymphocyte subsets, eosinophils, monocytes and mast cells.14,17 MCP-1 is expressed and released by a variety of cell types, including leucocytes, smooth muscle cells, endothelial cells, fibroblasts, epithelial cells, and alveolar macrophages, and is revealed to have selective chemotactic activity of mononuclear phagocytes and lymphocytes.7,9,18 MIP1-α is produced by appropriately stimulated T cells, alveolar macrophages, neutrophils, monocytes, airway epithelial cells, and fibroblasts, and has been shown to have chemotactic activity in T cells and monocytes.8,19 We have therefore hypothesized that these chemokines also mediate the recruitment of inflammatory cells to the lung in NSIP.

In this study, we measured the BAL fluid levels of RANTES, MCP-1 and MIP1-α in patients with NSIP, UIP and sarcoidosis to evaluate the contribution of these chemokines, and to determine whether there is a distinct profile of these chemokines in the diseases.

Materials and methods

Study population

The subjects of this study were patients and healthy volunteers enrolled in the Hospitals of Nagasaki University School of Medicine. The subjects included 20 patients with idiopathic UIP (16 males and 4 females; mean age, 61 years; age range 34–73), 15 with idiopathic NSIP (8 males and 7 females; mean age, 52 years; age range 28–72), 22 with pulmonary sarcoidosis (11 males and 11 females; mean age, 49 years; age range 23–75), and 12 healthy volunteers (8 males and 4 females; mean age, 26 years; age range 19–65). None of these patients had received steroid therapy at the time of clinical sample collection. Patients with cancer in any organ and those suspected to have malignancy were excluded from the study, and no malignancy was detected in any patient during the study. The diagnosis was pathologically confirmed by surgical lung biopsy in all patients with UIP and NSIP. Patients with UIP and NSIP associated with collagen vascular diseases were excluded in this study. The patients with sarcoidosis with pulmonary lesions were also enrolled in the study. The diagnosis was clinically established based on the pathological findings of noncaseous epithelioid cell granulomas in biopsy samples from lungs. The mean %VC was significantly lower in NSIP (76.7 ± 18.3%, P < 0.01) and UIP (79.4 ± 22.9%, P < 0.01) than in sarcoidosis (97.9 ± 20.0%) (Table 1), but there were no significant differences in mean %VC between UIP and NSIP. All healthy volunteers had normal chest radiographs, were free of symptoms and were not taking any medications. The study protocol was approved by the Human Ethics Review Committees of Nagasaki University School of Medicine, and a signed consent form was obtained from each subject.

Bronchoalveolar lavage and cell preparation

Informed consent was obtained from all patients and healthy volunteers, and BAL fluid samples were...
obtained from all subjects. BAL was performed as described previously using a flexible fiberoptic bronchoscope (Olympus IT-200, Olympus, Tokyo, Japan) after local anaesthesia of the upper airway with 4% lidocaine. Briefly, the bronchoscope was wedged for lavage into one of the subsegmental bronchi of the right middle lobe or, in patients with peripheral opacities, into areas of lung parenchyma otherwise normal on the chest radiograph. BAL was performed four times using 50 ml aliquot of sterile physiologic saline solution at body temperature. The BAL fluid was passed through two sheets of gauze and then centrifuged at 500g for 10 min at 4°C. The remaining fluid was centrifuged at 500g for 5 min, and the supernatant was stored at −80°C for further quantification of noncellular components. After washing twice with phosphate-buffered saline solution (PBS), cells were suspended with 10% heat-inactivated foetal calf serum and counted using a haemocytometer. Differential cell counts were determined from cell suspensions displayed on slides using a cytocentrifuge (CytoSpin 2; Shandon Instruments; Sewickley, PA). The cells were dried, fixed on the slide, and then stained by the May-Grunwald-Giemsa method. Two hundred cells were identified under a photomicroscope. Subsets of lymphocytes in BAL fluid were examined by direct immunofluorescence staining using fluorescein isothiocyanate-labelled murine monoclonal anti-CD3, CD4 and CD8 antibodies (Becton Dickinson; Mountain View, CA). The stained cells were analysed on a flow cytometer (FACScan; Becton Dickinson, FACS Division).

Measurement of RANTES, MIP-1α and MCP-1

Samples of BAL fluid were concentrated by Centriprep-3 (Millipore Corporation; Billerica, MA), which is used to concentrate low-molecular-weight components. The cut-off value for molecular weight is 3000 Da. In this procedure, the recovery of each CC chemokines was 80%, and the magnification of concentration was calculated by the ratio of protein consistency in nonconcentrated BAL fluid to concentrated BAL fluid, which was measured using assay (DC protein Assay; Bio-Rad Laboratories; Hercules, CA), and the original level of chemokines was corrected by this ratio. The levels of RANTES, MIP-1α and MCP-1 in BAL fluid were measured by commercially available enzyme-linked immunosorbent assay kits (Quantikine; R&D systems, Minneapolis, MN) according to the protocols provided by the manufacturer. The detection limits were 2.5, 5.0, 2.0 pg/ml for RANTES, MIP-1α, and MCP-1, respectively. Since BAL producer has a dilutional effect on the recovery of chemokines, measurements are occasionally standardized to albumin. A good correlation was observed between the non-standardized and standardized values by albumin concentrations in BAL fluid (data not shown), so the chemokine levels reported in the text are those of measured concentrations rather than those relative to albumin concentrations.

Statistical analysis

All values were expressed as mean ± standard deviation (SD) or range. Differences between multiple groups were compared by one-way analysis of variance. The post hoc test used was Fisher’s PLSD test. We also used Spearman’s rank correlation analysis to examine the relationship. Statistical analysis was performed using StatView-J 4.5 software (Abacus Concepts; Berkeley, CA). Statistical significance was defined by a P value of less than 0.05.

Results

Differential cell count of BAL fluid

Table 2 shows the characteristics of cells in BAL fluid in all subjects. Cell recovery in patients with UIP, NSIP and sarcoidosis is significantly higher than in normal controls (P<0.01). In patients with UIP, the percentages of macrophages were significantly higher than those in patients with NSIP and sarcoidosis (P<0.05). The percentages of lymphocytes in patients with NSIP and sarcoidosis were significantly higher than in patients with UIP and normal controls (P=0.01). The percentages of neutrophils and eosinophils in UIP patients were significantly higher than NSIP (P<0.05), UIP patients and normal subjects (P<0.01). The CD4/CD8 ratio in lymphocyte subsets in patients with sarcoidosis was significantly the highest among all subjects (P<0.01).

BAL fluid levels of RANTES, MIP-1α and MCP-1

As shown in Fig. 1, the levels of RANTES in BAL fluid were significantly higher in patients with NSIP (39.6 ± 14.6 pg/ml) compared with healthy volunteers (3.2 ± 2.1 pg/ml, P<0.01), UIP (12.3 ± 18.0 pg/ml, P<0.05) or sarcoidosis (14.7 ± 34.4 pg/ml, P<0.05). In MCP-1, the levels in BAL fluid of NSIP (208.3 ± 241.7 pg/ml) and UIP patients (153.4 ± 151.4 pg/ml) were significantly elevated compared with healthy volunteers (12.3 ± 9.0 pg/ml, P<0.01), UIP patients and normal controls (P=0.01). The percentages of neutrophils and eosinophils in UIP patients were significantly higher than NSIP (P<0.05), UIP patients and normal subjects (P<0.01). The CD4/CD8 ratio in lymphocyte subsets in patients with sarcoidosis was significantly the highest among all subjects (P<0.01).
ml, \( P<0.01 \) and sarcoidosis patients (36.9 \( \pm \) 44.4 pg/ml, \( P<0.01 \)). There were no significant differences in the levels of MIP-1\( \alpha \) in BAL fluid among the groups.

### Correlations between chemokine levels in BAL fluid and clinical data

Since C–C chemokines are chemotactic factors for lymphocytes, macrophages, and eosinophils, we examined the association in the paired samples between C–C chemokines and BAL fluid cells obtained from the patients. In NSIP, significant correlations were observed between the CD4/CD8 ratio or the percentage of CD8 cells and the levels of RANTES in BAL fluid (Table 3). In sarcoidosis, MCP-1 levels correlated with the percentages of lymphocytes and the numbers of eosinophils (\( r=0.472, P<0.05 \)) in BAL fluid. MIP-1\( \alpha \) levels also correlated with the number of lymphocytes (\( r=0.424, P<0.05 \)) and the percentages and numbers (\( r=0.546, P<0.05 \)) of neutrophils, and the number of eosinophils (\( r=0.571, P<0.01 \)) in BAL fluid of patients with sarcoidosis. RANTES levels also correlated with the percentage of neutrophils in BAL fluid of patients with sarcoidosis. In UIP, correlations were also tested between chemokine levels and the percentage and number of macrophages, lymphocytes, neutrophils, and eosinophils in BAL fluid, but no association was found (data not shown). However, there was a significant correlation between RANTES levels in BAL fluid and %VC (\( r=0.565, P<0.05 \)), FEV\(_1\)% (\( r=0.733, P<0.02 \)) or %DLCO (\( r=0.623, P<0.05 \)) in UIP. In addition, significant correlations were observed between MCP-1 levels in BAL fluid and %VC (\( r=0.558, P<0.05 \)), FEV\(_1\)% (\( r=0.743, P<0.02 \)), or PaO\(_2\) (\( r=0.705, P<0.01 \)) in patients with UIP. In patients with sarcoidosis, there were significant correlations between %VC and RANTES (\( r=0.707, P<0.02 \)), MCP-1 (\( r=0.577, P<0.05 \)), or MIP-1\( \alpha \) (\( r=0.664, P<0.02 \)). However, there was no significant correlation between these chemokines and pulmonary function tests in patients with NSIP.

### Discussion

The major finding in this study was that patients with NSIP and UIP had elevated concentrations of RANTES and MCP-1 in BAL fluid. The BAL fluid levels of RANTES in NSIP also increased significantly compared with UIP and sarcoidosis. One of the distinct clinical features of NSIP is a better prognosis than that of UIP.\(^1\)\(^-\)\(^3\) It is therefore important to clarify the differences of pathogenesis between UIP and NSIP. The present finding of lymphocytosis in BAL fluid of NSIP patients compared with UIP is consistent with previous reports.\(^4\)\(^-\)\(^6\) An accumulation of lymphocytes in the airways of patients with NSIP suggested that cytokines and chemokines contribute to chemotaxis of inflammatory cell and activation in NSIP. In this context, Park and colleagues demonstrated that

<table>
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<th>Cell recovery ( \times 10^5 ) (ml)</th>
<th>Normal subjects</th>
<th>NSIP (n = 15)</th>
<th>UIP (n = 20)</th>
<th>Sarcoidosis (n = 22)</th>
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<tr>
<td>Cell differentials</td>
<td></td>
<td></td>
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<tr>
<td>Macrophages (%)</td>
<td>83.7 ( \pm ) 14.4</td>
<td>58.2 ( \pm ) 21.0(^a)</td>
<td>75.4 ( \pm ) 13.2(^b)(^c)</td>
<td>55.5 ( \pm ) 23.6(^a)</td>
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<td>Lymphocytes (%)</td>
<td>15.0 ( \pm ) 13.9</td>
<td>34.1 ( \pm ) 20.3(^a)(^b)(^d)</td>
<td>13.8 ( \pm ) 9.6</td>
<td>41.9 ( \pm ) 23.2(^a)(^d)</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>0.9 ( \pm ) 1.0</td>
<td>3.2 ( \pm ) 3.3</td>
<td>5.6 ( \pm ) 6.3(^a)(^b)(^c)</td>
<td>1.3 ( \pm ) 1.8</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>0.4 ( \pm ) 0.8</td>
<td>2.2 ( \pm ) 2.6</td>
<td>5.2 ( \pm ) 7.5(^a)(^b)(^c)</td>
<td>1.0 ( \pm ) 0.1</td>
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<td><strong>Lymphocyte subsets</strong></td>
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<tr>
<td>CD3 (%)</td>
<td>72.7 ( \pm ) 25.0</td>
<td>84.8 ( \pm ) 18.5</td>
<td>85.5 ( \pm ) 14.3</td>
<td>90.1 ( \pm ) 7.3</td>
</tr>
<tr>
<td>CD4 (%)</td>
<td>34.6 ( \pm ) 12.3</td>
<td>27.8 ( \pm ) 15.9(^c)(^d)</td>
<td>46.5 ( \pm ) 20.3</td>
<td>57.2 ( \pm ) 22.7(^a)</td>
</tr>
<tr>
<td>CD8 (%)</td>
<td>45.0 ( \pm ) 11.6</td>
<td>56.5 ( \pm ) 21.8(^c)(^d)</td>
<td>39.2 ( \pm ) 17.8</td>
<td>29.9 ( \pm ) 19.9(^a)</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>0.9 ( \pm ) 0.5</td>
<td>0.7 ( \pm ) 0.7</td>
<td>1.6 ( \pm ) 1.3</td>
<td>3.0 ( \pm ) 2.1(^a)(^b)(^d)</td>
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Data are mean \( \pm \) SD.

\(^a\)Compared with normal subjects (\( P<0.01 \)).
\(^b\)Compared with NSIP (\( P<0.05 \)).
\(^c\)Compared with sarcoidosis (\( P<0.01 \)).
\(^d\)Compared with UIP (\( P<0.01 \)).
\(^e\)Compared with UIP (\( P<0.05 \)).
the lymphocytosis in the lesion of patients with NSIP is associated with the increased amount of IL-6 produced by the epithelial cells and the macrophages. The C–C chemokines such as RANTES, MCP-1, and MIP-1α are also the major candidates for inflammatory cell attraction to the lung in NSIP. RANTES, which is a potent eosinophil and lymphocyte attractant with particular preference for CD45RO+ T cells, is thought to contribute to the influx of inflammatory cells to the lung in interstitial lung diseases. Petrek and colleagues demonstrated that RANTES is expressed at the protein and mRNA level in the lower respiratory tracts of patients with interstitial lung diseases, that it is associated with the accumulation of memory T-cells within the lung, and importantly that the major sites of RANTES synthesis are macrophages alone in sarcoidosis, but macrophages and eosinophils in fibrosing alveolitis. Kodama and colleagues also demonstrated that the expression of RANTES mRNA by BAL fluid cells and the levels of RANTES protein in BALF were significantly increased in patients with IPF, sarcoidosis, and interstitial pneumonia associated with collagen vascular

![Figure 1](image-url) BAL fluid concentrations of RANTES (A), MCP-1 (B), and MIP-1α (C) in patients with various lung diseases and healthy volunteers. UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia.
diseases (CVD-IP) compared with healthy volunteers.\textsuperscript{11} In our study, the levels of RANTES in BAL fluid of NSIP were significantly higher than those in UIP and sarcoidosis. This finding suggests that RANTES may also mediate inflammatory cell influx in NSIP. Petrek and colleagues reported that an association was observed between RANTES mRNA, both absolute and relative number of CD4\textsuperscript{+} lymphocytes and also between this chemokine and CD4/CD8 ratio in patients with sarcoidosis.\textsuperscript{16} It is therefore possible that RANTES is also involved in the recruitment of CD4\textsuperscript{+} cells in NSIP. However, the percentage and number of lymphocytes and CD4 positive cells did not correlate with the RANTES levels in BALF of patients with NSIP as well as sarcoidosis in this study. It could be due to the relatively small numbers of patients used in this study. An additional clinical study will need to rectify this problem.

In interstitial lung diseases, MCP-1 also appears to be an important factor in the monocyte/macrophage-mediated inflammatory process. Suga et al. demonstrated that BAL fluid levels of MCP-1 in patients with IPF, IP-CVD and sarcoidosis were significantly higher than in controls, and that the level of MCP-1 in IPF was significantly higher than that those in other interstitial lung diseases.\textsuperscript{13} In lung tissues from IPF, metaplastic epithelial cells, alveolar and interstitial macrophages, and vascular endothelial cells are the major MCP-1 producing cells.\textsuperscript{7,9} Thus, MCP-1 has been implicated predominantly in IPF rather than in sarcoidosis. Our finding demonstrating the elevated levels of MCP-1 in IPF patients compared with sarcoidosis patients and controls is consistent with previous reports.\textsuperscript{13} In our study, the levels of MCP-1 in BAL fluid of IPF patients also correlated well with %VC, FEV\textsubscript{1}%, or PaO\textsubscript{2}. These findings suggest that MCP-1 may play an important role in the pathogenesis of IPF. In sarcoidosis, no significant differences were observed in the levels of MCP-1 compared with controls. However, MCP-1 levels in BAL fluid of patients with sarcoidosis correlated significantly with the percentages of lymphocytes and the numbers of eosinophils. These also correlated with %VC. These findings suggest that MCP-1 may also play an important role in the pathogenesis of sarcoidosis while it may be smaller than in IPF. This is supported by the findings reported by Petrek et al. demonstrating that MCP-1 mRNA expression was upregulated in sarcoidosis, particularly in patients with more advanced disease.\textsuperscript{16} Hashimoto and colleagues have also reported that plasma MCP-1 levels in patients with active sarcoidosis were significantly higher than in controls and the changes in MCP-1 were closely related to the clinical course of sarcoidosis.\textsuperscript{12} In NSIP, the levels of MCP-1 in BAL fluid were significantly higher than those in controls and sarcoidosis patients, but there were no correlations between MCP-1 levels and BAL cells or pulmonary function tests in this study. Therefore, it remains unclear as to whether MCP-1 is a key factor in NSIP as well as UIP.

MIP-1\textalpha has been found to show augmented expression in BAL fluid of both IPF and sarcoidosis patients.\textsuperscript{8,16} MIP-1\textalpha is also expressed in the lungs and promotes leucocyte accumulation and activation, leading to fibrosis in bleomycin-treated mice.\textsuperscript{22} Treatment of bleomycin-challenged mice with anti-MIP-1\textalpha antibody reduced accumulation of pulmonary mononuclear phagocytes and fibrosis.\textsuperscript{22} MIP-1\textalpha preferentially mediates chemotaxis of CD8\textsuperscript{+} cells into the lung in NSIP. However, there were no significant differences in the levels of MIP-1\textalpha in BAL fluid among the groups in this study. This is consistent with a report by Petrek and colleagues demonstrating that MIP-1\textalpha mRNA was present but

\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
 & NSIP &  &  & UIP &  &  & Sarcoidosis &  \\
 & MCP-1 & MIP1-\(\times\) & RANTES & MCP-1 & MIP1-\(\times\) & RANTES & MCP-1 & MIP1-\(\times\) & RANTES \\
\hline
Macrophages (\%) & 0.066 & 0.058 & 0.444 & 0.007 & 0.001 & 0.128 & -0.469 & -0.454 & 0.046 \\
Lymphocytes (\%) & 0.108 & 0.186 & 0.363 & 0.167 & 0.223 & 0.251 & 0.456 & 0.404 & < 0.01 \\
Neutrophils (\%) & 0.259 & 0.268 & 0.301 & 0.021 & 0.363 & 0.045 & 0.054 & 0.480 & 0.805 \\
Eosinophils (\%) & 0.194 & 0.404 & 0.064 & 0.181 & 0.011 & 0.140 & 0.191 & 0.306 & 0.114 \\
CD4 (\%) & 0.451 & 0.028 & -0.639 & 0.124 & 0.238 & 0.070 & 0.083 & 0.162 & 0.124 \\
CD8 (\%) & 0.266 & 0.180 & 0.666 & 0.180 & 0.039 & 0.008 & 0.162 & 0.149 & 0.135 \\
\hline
\end{tabular}

\(\textsuperscript{*}P < 0.05\).
not upregulated in BAL fluid cells from sarcoidosis patients.\textsuperscript{16} They and others\textsuperscript{23} also could not detect MIP-1\(\alpha\) protein in BAL fluid from sarcoidosis patients. These data suggest that MIP-1\(\alpha\) does not contribute to inflammatory cell recruitment into the lung in these diseases. However, MIP-1\(\alpha\) levels of BAL fluid of patients with sarcoidosis correlated with the number of lymphocytes in BAL fluid and \%VC in this study. Further studies are therefore required to define the role of MIP-1\(\alpha\) in interstitial lung diseases.

In conclusion, an elevation of RANTES and MCP-1 levels in BAL fluid was seen in NSIP while these levels did not correlate with any clinical data including BAL fluid cells and pulmonary function tests. These results suggest that cytokine and chemokine storm may occur in the lung of NSIP patients, but other main mediators, e.g. IL-6,\textsuperscript{5} may mainly play an important role in the pathogenesis of NSIP.

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