
◎原 著

Immunosuppression by glucocorticoids leads to bronchoalveolar neutrophilia in patients with bronchial asthma

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Abstract : Cellular composition of bronchoalveolar lavage (BAL) fluid was compared between two age-matched steroid-dependent intractable asthma (SDIA) groups : 17 group A patients (serum IgG level $< 1000\text{mg/dl}$) whose immunity was regarded as being suppressed by long-term glucocorticoid therapy and 17 group B patients (serum IgG level $> 1200\text{mg/dl}$). 1. The levels of serum IgA and IgM were significantly decreased in group A compared to the levels in group B patients. 2. The number of blood lymphocytes was also significantly lower in group A than in group B patients. However, the number of blood neutrophils was not different between the two asthma groups. 3. The number of BAL lymphocytes was significantly lower in group A than in group B patients. 4. BAL neutrophilia (more than $1.5 \times 10^4/\text{ml}$) was observed in 6 of the 17 (35.3%) patients in group A, but not observed in any patients in group B. The number of BAL neutrophils was significantly greater in group A than in group B patients.

These results suggest that there is a correlation between immunosuppression by glucocorticoids and BAL neutrophilia in patients with bronchial asthma.

Key words : immunosuppression, BAL neutrophilia, glucocorticoids, bronchial asthma

Introduction

Recent studies on analysis of cellular and humoral events in bronchoalveolar (BAL) fluid have demonstrated that airway

inflammation is a common feature of bronchial asthma (1-5). Airway inflammation which consists of inflammatory cells such as lymphocytes (6-8), neutrophils (9), eosinophils (10, 11), and basophils, is related to

the severity of asthma (12).

Asthma is classified into three clinical types according to symptoms and signs: Ia. simple bronchoconstriction type, Ib. bronchoconstriction+hypersecretion type, and II bronchiolar obstruction type (13–15). Of these three asthma types, type II asthma is characterized by an increased number of bronchoalveolar neutrophils and marked decrease in the values of ventilatory parameters. An increased number of BAL neutrophils is sometimes observed in asthmatic patients with long-term glucocorticoid therapy (16). These findings suggest that there is a correlation between long-term glucocorticoid therapy and an increased number of BAL neutrophils in patients with bronchial asthma.

Long-term glucocorticoid regimen brings about many side effects such as hypertension, diabetes mellitus, osteoporosis, muscle weakness, suppression of adrenocortical glands and suppression of humoral and cellular immunity. Of these side effects, immunosuppression by glucocorticoids may affect inflammatory process in the airways of asthma and be related to asthma severity.

In the present study, a correlation between immunosuppression by glucocorticoids and BAL neutrophilia was examined in patients with steroid-dependent intractable asthma (SDIA).

Subjects and Methods

The subjects of this study were 34 patients with bronchial asthma (17 females and 17 males, mean 53.0 years, range 21–71 years). The mean level of serum IgE was 428 IU/ml (range 11–3058 IU/ml). All the subjects were non-smokers, and they were regarded as having steroid-dependent intractable asthma (SDIA), since they had been treated with

glucocorticoids for more than 2 years. The subjects were divided into two groups according to the level of serum IgG: less than 1000 mg/dl (group A) and more than 1200 mg/dl (group B). The patients in group A were regarded as their immunity being suppressed by glucocorticoids, and in group B patients the immunity was not suppressed.

Bronchoalveolar lavage (BAL) was performed after informed consent was obtained from all the subjects. The BAL was carried out in all study subjects by a previously reported method (14, 15) when their attacks were atable with prednisolone of 5 mg/day or less. Briefly, the aspirates were centrifuged at 1200 rpm for 10 min at 4°C after filtration through a sterile steel mesh, and the resultant cell pellet was resuspended in Tris ACM. After total cell number was counted, smear preparations made with the cell suspensions were stained with May Giemsa. A differential cell count was performed on 500 cells, excluding epithelial cells. In the present study, the mean recovery rate at BAL was $2.65 \pm 11.4\%$ (\pm SD), and the total cell number was $7.0 \pm 3.0 \times 10^6$. The results were expressed as /ml.

The levels of serum IgG, IgA, and IgM were measured by turbidometric immunoassay. Serum IgE level was estimated by radioimmunosorbent test (RIST).

Results

Table 1 shows characteristics of patients with bronchial asthma divided by the level of serum IgG. In this study, 17 patients whose immunity was suppressed by long-term glucocorticoid therapy were at first selected, and then 17 age-matched asthma patients whose serum IgG level was more than 1200 mg/dl (regarded as not being suppressed by

glucocorticoids) were selected. Thus, the mean age in the two groups was almost same. Serum IgE level was higher in patients of group B than in those of group A, although this difference was not significant. The levels of serum IgA and IgM were significantly lower in patients of group A than in those of group B (IgA : $p < 0.02$; IgM : $p < 0.01$). Distribution of serum IgG levels in groups A and B was shown in Fig. 1.

Table 1. Characteristics of patients with bronchial asthma studied

Asthma group	No of patients	Age (yr)	Serum levels of			
			IgE*	IgG**	IgA**	IgM**
A	17	52.9	306 ±356	873 ±118	194 ^a ± 65	136 ^b ±104
B	17	53.1	531 ±733	1402 ±195	246 ^a ± 53	224 ^b ± 67

Group A: patients with serum IgG level of less than 1000 mg/dl; B: patients with serum IgG level of more than 1200 mg/dl. *IU/ml, **mg/dl. a: $p < 0.02$; b: $p < 0.01$.

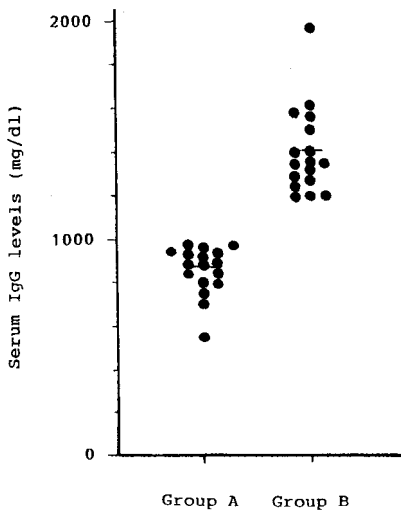


Fig. 1. Serum IgG levels in patients with bronchial asthma. Group A : patients with serum IgG level of less than 1000 mg/dl ; B : patients with serum IgG levels of more than 1200 mg/dl.

Immunosuppressive action of glucocorticoids can be observed in serum immunoglobulin concentrations and blood cell count in peripheral blood. The number of blood neutrophils was not different between groups A (4808 ± 1286 /cmm) and B (4576 ± 1419 /cmm), as shown in Fig. 2. The number of blood lymphocytes was significantly decreased in group A patients (serum IgG level less than 1000 mg/dl) compared to that in group B patients ($p < 0.01$) (Fig. 3).

Table 2 shows the results of BAL examinations. Total cell number and recovery rate at BAL were slightly greater in group B than in group A subjects, although this was not significant.

The number of BAL macrophages was not significantly different between groups A and B (Fig. 4). The number of BAL lymphocytes was decreased in group A patients, which was

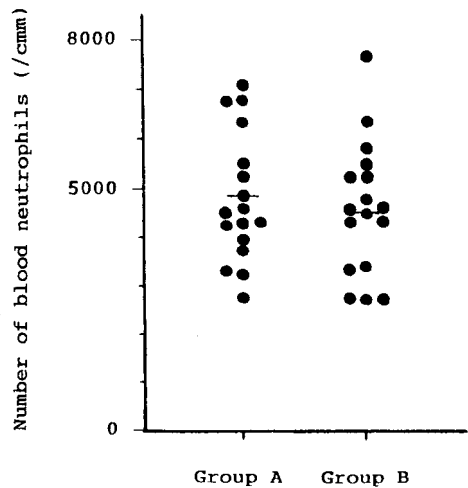


Fig. 2. Number of blood neutrophils in patients with bronchial asthma. Group A : patients with serum IgG level of less than 1000 mg/dl ; B : patients with serum IgG level of more than 1200 mg/dl.

significantly lower than that in group B patients ($P < 0.05$) (Fig. 5). BAL neutrophilia (more than $1.5 \times 10^4 / \text{ml}$) was observed in 6 of the 17 (35.3%) patients in group A, but in none of them in group B. The mean number of BAL neutrophils was significantly greater in group A than in group B patients ($p < 0.05$) (Fig. 6, Table 2).

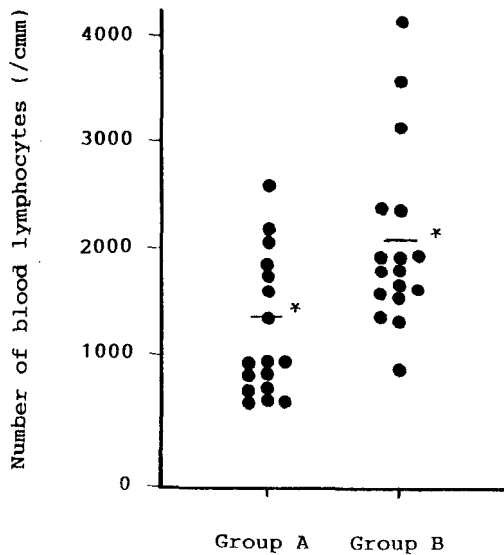


Fig. 3. Number of blood lymphocytes in patients with bronchial asthma. Group A : patients with serum IgG level of less than 1000 mg/dl ; group B : patients with serum IgG level of more than 1200 mg/dl. *p < 0.01.

Table 2. BAL examination results in patients with bronchial asthma studied

Asthma group	Recovery rate	Total cell number ($\times 10^6$)	BAL cells ($10^4 / \text{ml}$)			
			Mac	Lym	Neut	Eos
A	24.7 ± 10.1	6.2 ± 2.8	11.8 ± 12.2	1.24 ^a ± 1.18	3.44 ^b ± 5.7	3.5 ± 5.1
B	28.4 ± 12.2	7.7 ± 3.1	14.5 ± 6.4	3.13 ^a ± 1.56	0.36 ^b ± 0.31	1.55 ± 2.55

Group A: patients with serum IgG level of less than 1000 mg/dl; B: patients with serum IgG level of more than 1200 mg/dl. Mac, macrophages; Lym, lymphocytes; Neut, neutrophils; Eos, eosinophils. a:p < 0.001; b:p < 0.05.

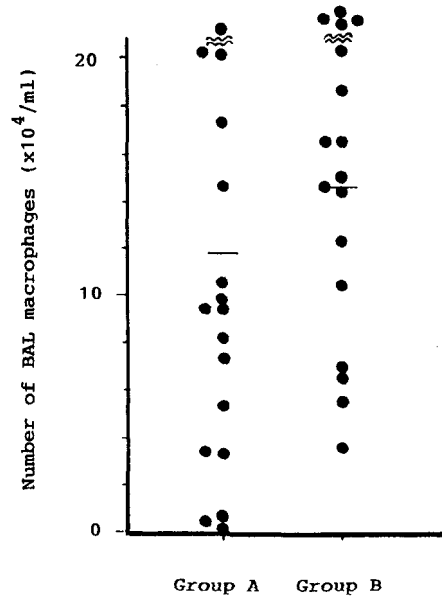


Fig. 4. Number of BAL macrophages in patients with bronchial asthma. Group A : patients with serum IgG level of less than 1000 mg/dl ; group B : patients with serum IgG level of more than 1200 mg/dl.

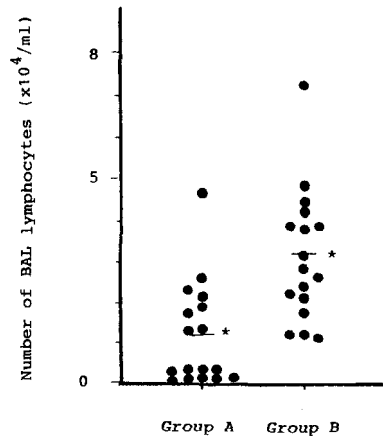


Fig. 5. Number of BAL lymphocytes in patients with bronchial asthma. Group A : patients with serum IgG level of less than 1000 mg/dl ; group B : patients with serum IgG level of more than 1200 mg/dl. *p < 0.001.

lymphocytes, and in such patients with suppressed immunity BAL neutrophilia is often observed. In these conditions, asthma is severe and difficult to control.

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気管支喘息における副腎皮質ホルモン長期投与による免疫抑制と気管支肺胞洗浄液中好中球増多との関連

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ステロイド依存性重症難治性喘息を, 免疫抑制の見られる症例(血清IgG値 1000 mg/dl 以下)(グループA)と抑制の見られない症例(血清IgG値 1200 mg/dl 以上)(グループB)の2群に分け, 気管支肺胞洗浄液中の細胞成分について比較検討した。

1. 血清IgAおよびIgM値は, グループBに比べ免疫抑制の見られるグループAにおいて有意に低い値であった。

2. 末梢血リンパ球数は, グループAにおいて, グループBに比べ有意に少ない傾向が見られた。しかし, 末梢血好中球数は両群間に有意の差は見られなかった。

3. BAL液中リンパ球数は, グループBに比べ免疫抑制の見られるグループAにおいて有意に少ない数であった。

4. BAL液中好中球増多($1.5 \times 10^4 / \text{ml}$ 以上)を示す症例は, グループAの17例中6例(35.3%)に見られたが, グループBでは全く見られなかった。また, BAL液中好中球数は, グループAにおいてグループBに比べ有意に多い数であった。

以上の結果により, 副腎皮質ホルモン長期投与による免疫抑制とBAL液中好中球増多とはある程度関連があることが明らかにされた。

キーワード: 免疫抑制, BAL好中球増多, 副腎皮質ホルモン, 気管支喘息