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Transient bronchoalveolar neutrophilia in a patient with atopic asthma

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Abstract : Clinical course of one asthma patient (64 years old, female), who had an increased proportion of neutrophils in bronchoalveolar lavage (BAL) fluid, was observed in relation to the proportion of BAL cells and ventilatory function. The patient had large asthma attacks two times during her clinical course for 15 months observed. 1. An increased proportion of BAL neutrophils and suppression of ventilatory function were found after her first large asthma attacks. The increased proportion of BAL neutrophils continued for more than 5 months. A reduction in the proportion of BAL neutrophils was found 3 months after her second large asthma attack, accompanied by improvement of clinical symptoms and ventilatory function. The numbers of total cells and neutrophils in BAL fluid were also reduced. Transient increase in number of BAL lymphocytes was found 13 months after the first large attack when the number of BAL neutrophils was markedly decreased. The number of BAL eosinophils did not change during her clinical course.

Key words : Bronchial asthma, transient BAL neutrophilia, ventilatory function

Introduction

Recently, airway inflammation in patients with bronchial asthma has been noted as a major mechanism causing asthma attacks. In the inflammatory process, lymphocytes, neutrophils, eoosinophils, and basophils, which migrate from the bloodstream, play their important roles in the mechanism of onset of the disease (1−7) . Of these cells, lymphocytes, eosinophils and basophils have been clarified to participate in pathophysiological changes in the airways of asthma, since these cells are activated in allergic

reaction sites and release lymphokines or chemical mediators (8－13). However, it is still uncear whether neutrophils in the airways participate in the mechanism of onset of asthma. Our previous studies have shown that an increased proportion of neutrophils in bronchoalveolar lavage (BAL) fluid was sometimes found in patients with asthma, particularly in those with steroid-dependent intractable aasthma (SDIA) (14,15). Our studies have also demonstrated that an increased proportion of BAL neutrophils in asthma patients is closely related to long-term glucocorticoid therapy (15).

In the present study, clinical characteristics of a patient who showed transient increase in the proportin of BAL neutrophils were examined in relation to clinical symptoms, the proportion of BAL cells, and ventilatory function.

Table 1. Allergo-immunological examinations

Immunoglobulins		**Lympocyte subsets**	
IgE	504 IU/mℓ	CD4	52%
IgG	1388mg/dℓ	CD8	20%
IgA	381mg/dℓ	CD4/8ratio	2.6
IgM	67mg/dℓ		
RAST score			
House dust 1	2+	**Blood cells**	
Mite1	3+	RBC	398×10^4/cmm
Candida	0+	Hb	12.2g/dℓ
		WBC	10600/cmm
Skin test		St	29%
House dust	+	Sg	53%
Japanese Cedar	+	Lym	13%
Silk	+	Mo	5%
Candida	−	Eo	0%
		Ba	0%

Case report

The patient was 64 years old, female, with atopic asthma. She had had asthma attacks, but not large, for 2 years before she was admitted to Katsuyama hospital (which was located at north side of Okayama prefecture) on April 7, 1988, because of her first large attack. On her admission to the hospital, she had various examinations for her asthma. The results of allergo-immunological examinations were shown in Table 1 : she was evaluated as atopic asthma, because the level of serum IgE was high and IgE antibodies to house dust mite was found in her serum. However, peripheral eosinophilia was not found on her admission.

When she was admitted to the hospital, she had large asthma attack in which breath sound were markedly decreased and moist rales (bubbling) were heard over both lower lung fields on auscultation. She complained of marked dyspnea and recurrent cough all day long, particularly at night. Clinical and laboratory findings on her admission, fever, yellowish sputum, increased number of peripheral neutropphils and a high value of CRP (13.5 mg／dℓ), showed that she had respiratory infection. Thus, she was treated with antibiotics, expectorants, bronchodilators and glucocorticoids. Her symptoms and laboratory findings were markedly improved 2 months after her admission and she was discharged on July 15, 1988. After then she had slight respiratory infection, which induced her second large asthma attack. Then she was admitted to our hospital, as shown in Fig. 1.

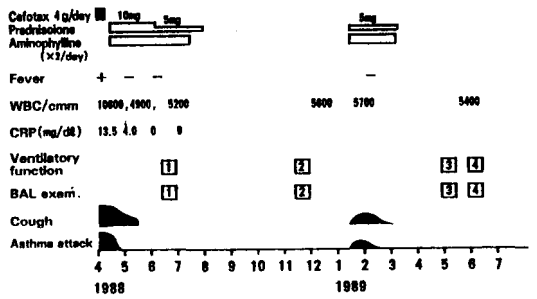

Fig. 1. Clinical course of the patient with atopic asthma (64 years old, female). The patient had large asthma attacks two times during her clinical course for 15 months observed. BAL examinations and ventilatory function tests were performed four times, as shown by the number in parenthesis.

BAL examination

Bronchoalveolar lavage (BAL) was performed four times during all her clinical course after her first large asthma attack, by a previously reported method (14−16). The proportion of BAL cells 2 months after her first large asthma attack was as follows : 33.0% macophages, 10.4% lymphocytes, 56.2 % neutrophils, 0.2% eosinophils, and 0.2% basophils. The results showed marked increase in the proportion of BAL neutrophils. The second BAL examination was performed 7 months after her first large asthma attack. Although she was free of attacks at that time, the second BAL examination results still showed marked increase in the proportion of BAL neutrophils. In the third BAL examination, which was performed 3 months after her second large asthma attack, the proportion of BAL neutrophils was markedly decreased : 45.2% macrophages, 48.6% lymphocytes, 5.6% neutrophils, and 0.6% eosinophils. Her clinical course was good and she had never asthma attacks after her second large asthma attack. The fourth BAL examination was carried out 4 months after her second large asthma attack (one month after the third BAL examination). The proportion of each BAL cell in this examination was 58.0% macrophages, 36.2% lymphocytes, 5.6 % neutrophils and 0.2% eosinophils These results show that reduction in the proportion of BAL neutrophils, which was accompanied by increase in the proportion of BAL lymphocytes, was found during her clinical course (Fig. 2).

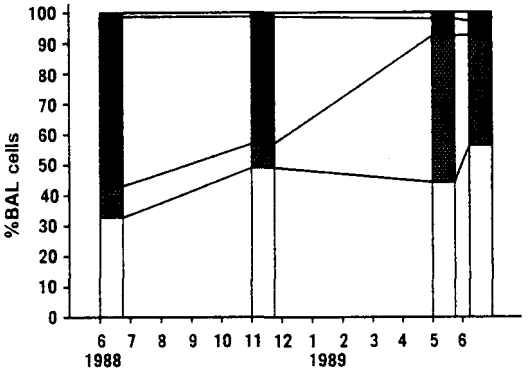

Fig. 2. Changes in the proportion of each BAL cell of the patient (64 years old, female) during her clinical course for 15 months observed. An increased proportion of BAL neutrophils was observed at the first and second BAL examination. After then the proportion of BAL neutrophils decreased and the proportion of BAL lymphocytes tended to increase. ( ) macrophages, ( ) lymphocytes, ( ) neutrophils, ( ) eosinophils.

Total cell number in BAL fluid was also reduced as the proportion of BAL neutrophils decreased, as shown in Table 2. The number of BAL lymphocytes was increased at the third BAL examination. The number of BAL neutrophils was reduced at the second BAL

examination, and markedly reduced at the third and fourth BAL examination. The number of BAL eosinophils did not change during all her clinical course (Table 2).

Table 2. Total cell number and number of each cell in bronchoalveolar lavage (BAL) fluid

BAL examination	Total cell number ($\times10^6$)	($\times10^4$/ml)	BAL cells ($\times10^4$/ml) Mac	Lym	Neut	Eos
1. June 20, 1988	18.8	31.3	10.3	3.3	17.6	0.1
2. November 14, 1988	18.6	25.8	12.8	2.0	10.9	0.1
3. April 5, 1989	12.3	12.4	5.6	6.0	0.7	0.1
4. June 6, 1989	9.9	7.4	4.2	2.7	0.4	0.1

Mac, macrophages; Lym, lymphocytes; Neut, neutrophils; Eos, eosinophils.

Ventilatory function

Ventilatory function tests, using a Box Spiror 81-S (Chest Co.), were carried out 4 times when she was free of attacks. In the first ventilatory function tests, which were performed 2 months after her first large asthma attack, the values of each ventilatory parameter were 2.30 ℓ in FVC, 1.28 ℓ in FEV1.0, 3.41 ℓ/sec in PEFR, 0.81 ℓ/sec in $\dot{V}_{50}$ and 0.26 ℓ/sec in $\dot{V}_{25}$, respectively, demonstrating marked decrease in the values of FEV1.0, $\dot{V}_{50}$ and $\dot{V}_{25}$. The results in the second ventilatory function tests (performed 7 months after her first large asthma attack) were similar to those in the first ventilatory function tests. These obstructive ventilatory dysfunction gradually improved as the proportion of BAL neutrophils decreased. The values of each ventilatory paramenter were 2.33 ℓ in FVC, 1.58 ℓ/sec in FEV1.0, 3.92 ℓ/sec in PEFR, 1.07 ℓ/sec in $\dot{V}_{50}$ and 0.35 ℓ/sec in $\dot{V}_{25}$ in the third ventilatory function tests which were performed 3 months after her second large asthma attack. The values of each ventilatory parameter were clearly improved 4 months after her second large asthma attack : 2.42 ℓ (+5.2%, compared to the value in the first ventilatory function tests) in FVC, 1.73 ℓ (+35.2%) in FEV1.0, 4.65 ℓ/sec (+36.4 %) in PEFR, 1.56 ℓ/sec (+92.6%) in $\dot{V}_{50}$ and 0.83 ℓ/sec (+219.2%) in $\dot{V}_{25}$, as shown in Fig. 3.

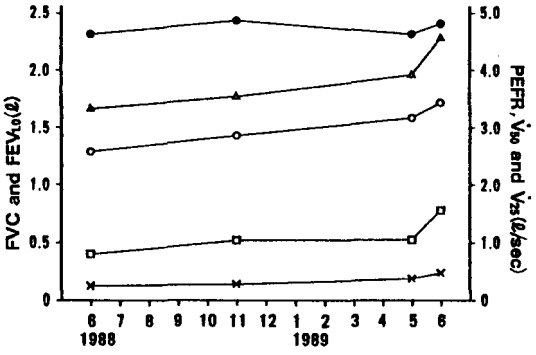

Fig. 3. Improvement of ventilatory function of the patient (64 years old, female) during her clinical course for 15 months observed. Percent improvement of each ventilatory parameter compared to the initial value after her first large asthma attack was +5.2% in FVC (●—●), +35.2% in FEV 1.0 (○—○), + 36.4% in PEFR (△—△) , +92.6% in $\dot{V}_{50}$ (□—□) and +219.2% in $\dot{V}_{25}$ (×—×) .

Discussion

Recently, airway inflammation has been considered to be important in the mechanism of asthma (1−7). It is necessary for inflammatory cells, which are observed in local allergic reaction sites, to be activated to play their roles. Of these inflammatory cells such

as lymphocytes, eosinophils and basophils, all cells except neutrophils have been shown to be activated at local allergic reaction sites and release lymphokines or chemical mediators (8−13). However, there are no evidences about activation of neutrophils in the airways (11,17). Furthermore, although there are a few reports about BAL neutrophilia in bronchial asthma (18), clinical significance of BAL neutrophils is unclear. Thus, it is unclear whether neutrophils participate in the mechanism of onset of asthma.

Table 3 shows 7 patients with bronchial asthma who had an increased proportion of BAL neutrophils (more than 50%). Case 1 in Table 3 is the patient whose clinical course was discussed in this study. The other six patients with bronchial asthma had glucocorticoid therapy for a long time. They were evaluated as having steroid-dependent intractable asthma (SDIA), and their symptoms have not been improved. They always require glucocorticoids for their asthma attacks. In none of them, the proportion of BAL neutrophils has not shown a tendency to decrease despite long-term treatment including glucocorticoids. In contrast, in case 1, the proportion of BAL neutrophils was reduced during her clinical course. Her symptoms and ventilatory function were clearly improved and she did not require glucocorticoids after her second large asthma attack. Of the 7 patients with an increased proportion of BAL neutrophils, as shown in Table 3, case 1 had not SDIA and showed transient BAL neutrophilia.

Table 3. Asthma patients with BAL neutrophils of more than 50%

Patients	Age	Sex	IgE (IU/ml)	RAST (HD)	Glucocorticoids Dose (mg/day)	Duration (years)
1.K·S.	64	F	504	2+	—	—
2.S·B.	56	F	105	—	7.5	4
3.T·H.	45	M	233	—	12.5+K	15
4.M·T.	71	M	108	—	7.5	6
5.H·O.	56	M	1820	2+	10.0	5
6.K·T.	52	M	65	—	20.0	12
7.T·F.	37	M	201	—	10.0+K	7

K : deposit type of glucocorticoids (Kenacort A®)

Our previous studies have demonstrated that bronchial asthma is classified into three clinical types : Ia. simple bronchoconstriction type, Ib. bronchoconstriction + hypersecretion type, and II. bronchiolar obstruction type (19, 20). Of these clinical asthma types, type Ib asthma is characterized by increased proportion of BAL eosinophils, and type II asthma is characterized by increased proportion of BAL neutrophils (14, 21−23). These findings suggest that an increased number of BAL neutrophils is closely related to clinical feature of type II asthma. Our previous studies have also shown that an incrrease in the proportion of BAL neutrophils is related to long-term oral glucocorticoid therapy (15). In these steroid-dependent intractable asthma, persistent BAL neutrophilia may be induced by long-time glucocorticoid regimen.

It was unclear in this study whether there are some differences between mechanisms causing transient and persistent BAL neutrophilia. Further studies are necessary to clarify mechanisms inducing BAL neutrophilia.

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気管支肺胞洗浄液中に一過性の好中球増多をきたしたアトピー型喘息

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経過中に気管支肺胞洗浄（BAL）液中に一過性の好中球増多が観察されたアトピー型喘息症例について，若干の臨床的観察を加えた。症例は，６４才の女性で，臨床症状，および血清IgE高値，ハウスダストに対するIgE抗体陽性などから，アトピー型喘息と診断された。なお，経過観察し得た15カ月の間に２回の大発作が観察された。

１．第１回の大発作後，BAL液中好中球増多と換気機能の低下が観察された。そして，このBAL 液中好中球頻度は明らかな改善が見られた。BAL液中の総細胞数および好中球の絶対数も徐々に減少傾向を示し，好中球頻度と同様，第2回目の大発作３カ月後には著明な減少が観察された。同時にこの時期には，BAL液中リンパ球の増加も見られた。しかし，BAL液中好酸球数は15カ月の経過観察中ほとんど変化は見られなかった。

キーワード：気管支喘息，一過性BAL液中好中球増多，換気機能