
◎原 著

Clinical features of type II asthma (bronchiolar obstruction) without bronchoalveolar neutrophilia

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Abstract : Clinical features of asthma patients with bronchiolar obstruction (type II asthma) were studied in relation to the proportion of neutrophils in bronchoalveolar lavage (BAL) fluid. Of 13 subjects studied, 7 were accompanied with BAL neutrophilia (53.5%) (BALn⁺) and 6 were without BAL neutrophilia (3.5%) (BALn⁻). 1. The mean age was higher in BALn⁻ (66.0 years) than in BALn⁺ patients (55.0 years). 2. Bronchial reactivity to methacholine was slightly higher in BALn⁻ patients than in those with BALn⁺. 3. The value of FEV_{1.0}% was significantly lower in BALn⁺ patients than in those with BALn⁻ ($p < 0.01$). 4. The proportion of BAL lymphocytes was significantly more decreased in BALn⁺ patients compared to the proportion in those with BALn⁻ ($p < 0.001$). 5. The values of serum IgG, IgA, and IgM were not significantly different between BALn⁺ and BALn⁻ patients, however, the value of IgG was more decreased in BALn⁺ patients than in those with BALn⁻.

These results suggest that two kinds of type II asthma; one is with BAL neutrophilia related to suppressed immunity, and another is without BAL neutrophilia in part due to aging.

Key words : Bronchial asthma, Bronchiolar obstruction, BAL neutrophilia, Suppressed immunity, Aging

Introduction

The major pathophysiological changes in the airways of bronchial asthma are bronchoconstriction, mucus hypersecretion, edema of mucous membrane, and bronchiolar obstruction. Our previous studies have shown that asthma is classified into three fundamental types; Ia. simple bronchoconstriction type, Ib. bronchoconstriction + hypersecretion

type, and II. bronchiolar obstruction type, according to these changes in the airways¹⁻⁵⁾. Of three asthma types, type II asthma (bronchiolar obstruction) is characterized by increased number of neutrophils and decreased lymphocyte count in bronchoalveolar lavage (BAL) fluid^{4, 5)}, which are often observed in asthma patients with long-term glucocorticoid therapy⁶⁻⁸⁾.

Airway inflammation, in which migration

of lymphocytes, eosinophils, neutrophils, and basophils into local allergic reaction sites is observed in patients with asthma⁹⁻¹². It has been suggested that activated T lymphocytes and eosinophils play an important role as inflammatory cells inducing asthmatic reaction^{13,14}. Furthermore, a role of neutrophils in the airways of asthma has been noted in recent years^{15,16}.

Increased number of BAL neutrophils may be caused by suppression of local and/or generalized humoral and cellular immunity^{7,8}. Thus, pathophysiology of type II (bronchiolar obstruction) asthma is closely related with BAL neutrophilia^{4,5}. However, our recent clinical observations have shown that there are some type II asthma patients without BAL neutrophilia.

In the present study, clinical features of type II asthma without BAL neutrophilia were analyzed, comparing to those of same type with BAL neutrophilia, in relation to patient age, bronchial hyperresponsiveness, ventilatory function, and BAL lymphocyte count.

Subjects and Methods

The subjects of this study were 13 asthma patients with bronchiolar obstruction (type II). Of these, 7 were patients with BAL neutrophilia (more than 10%) (BALn⁺), and 6 without BAL neutrophilia (BALn⁻). All patients had a long-term systemic glucocorticoid therapy for more than 2 years.

To evaluate type II asthma, classification of asthma by clinical symptoms (clinical diagnosis)^{2,4,5} was applied, but not classification by clinical findings and examinations (score diagnosis)³.

Bronchial reactivity to methacholine was measured by an Astograph (TCK 6100, Chest

Co)^{17,18}. Different concentrations of methacholine (49, 98, 195, 390, 781, 1563, 3125, 6250, 12500 and 25000 $\mu\text{g}/\text{ml}$) were prepared for bronchial challenge according to the method used by Chai et al¹⁹. The increase of total respiratory resistance (Rrs) after methacholine inhalation was measured by the oscillation method²⁰. A methacholine concentration causing a significant increase in Rrs was assessed as Cmin (minimum concentration). All medications were stopped 12 hours prior to examination.

BAL was carried out in all patients according to the method previously described when they were symptom free⁴⁻⁷, and informed consent for this examination was obtained from all study subjects.

Ventilatory function was carried out in all subjects at attack-free stage, using a Box Spiro 81 (Chest Co).

Serum IgE was measured by radioimmunosorbent test (RIST) and IgE antibodies were estimated by radioallergosorbent test (RAST).

Results

Table 1 shows characteristics of type II asthma patients with and without BAL neutrophilia. Mean age was higher in asthma patients without BAL neutrophilia (BALn⁻) than in those with BAL neutrophilia (BALn⁺). In contrast, mean age at onset of the disease was lower in BALn⁻ patients than in those with BALn⁺. The level of serum IgE was not significantly different between two asthma groups.

Bronchial reactivity to methacholine was slightly higher in BALn⁻ patients compared to that in those with BALn⁺, as shown in Fig. 1. However, this was not significant.

Table 1. Characteristics of type II asthma patients with and without BAL neutrophilia

	No of patients	Age (years)	Age at onset (years)	IgE (IU/ml)	BAL neutrophils (%)
BALn+	7	55.0	43.9	429 (103-1820)	53.5
BALn-	6	66.0	36.7	277 (68-890)	3.5

BALn+;patients with BAL neutrophilia, BALn-;patients without BAL neutrophilia

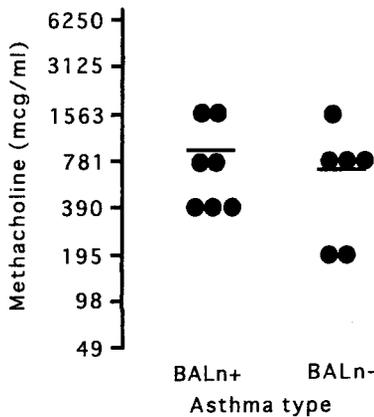


Fig. 1. Bronchial reactivity to methacholine in type II asthma with (BALn⁺) and without BAL neutrophilia (BALn⁻)

Figure 2 demonstrates comparison in the value of FEV 1.0% between two asthma groups. The value of FEV 1.0% was significantly lower in BALn⁺ patients than in those with BALn⁻ ($p < 0.01$).

The proportion of BAL lymphocytes was significantly higher in BALn⁻ than in BALn⁺ patients ($p < 0.001$), as shown in Fig. 3. In 6 of 7 (85.7%) BALn⁺ patients, the proportion of BAL lymphocytes was less than 10%.

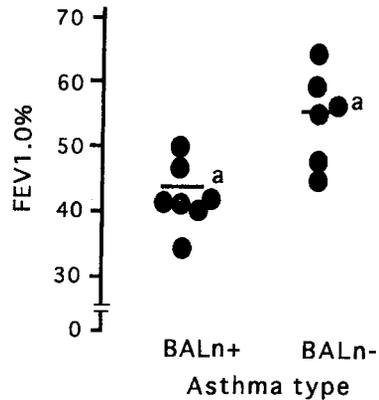


Fig. 2. Comparison in FEV1.0% between type II patients with (BALn⁺) and without BAL neutrophilia (BALn⁻). a; $p < 0.01$.

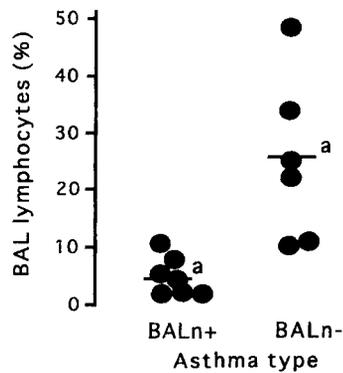


Fig. 3. Comparison in the proportion of BAL lymphocytes between type II patients with (BALn⁺) and without BAL neutrophilia (BALn⁻). a; $p < 0.001$.

Table 2 shows the levels of serum IgG, IgA and IgM in two asthma groups. The mean level of serum IgG was slightly lower in BALn⁺ patients than the level in those with BALn⁻, however, this difference was not significant. The levels of serum IgA and IgM

were not different between two asthma groups.

Table 2. Comparison in levels of serum IgG, IgA and IgM between type II patients with (BALn⁺) and without BAL neutrophilia (BALn⁻)

Asthma type	Serum levels (mg/dl)		
	IgG	IgA	IgM
BALn ⁺	911 ± 260	281 ± 37	153 ± 24
BALn ⁻	1004 ± 212	294 ± 55	113 ± 75

Discussion

Bronchial asthma is classified into three fundamental types by clinical pathophysiological changes in the airways such as bronchoconstriction, mucus hypersecretion, and bronchiolar obstruction; Ia. simple bronchoconstriction type, Ib. bronchoconstriction + hypersecretion type (expectoration, over 100ml/day), and II. bronchiolar obstruction type¹⁻⁵). Moreover, type Ia is divided into two subtypes according to expectoration per day. Ia-1(0-49 ml) and Ia-2(50-99ml)⁵).

Regarding the proportion of inflammatory cells, BAL eosinophilia is often found in type Ib (hypersecretion)^{2b}), and BAL neutrophilia in type II asthma (bronchiolar obstruction). The results reveal that pathogenesis of type II asthma is closely related to increased number of BAL neutrophils. Furthermore, BAL neutrophilia related to type II asthma is often observed in patients with long-term systemic glucocorticoid therapy, which often induces decreased number of peripheral lymphocytes and decrease in the level of serum

IgG. These lead to suppression of humoral and cellular immunity^{7, 8}). It has been suggested from these data that type II asthma may be caused by suppressed humoral and cellular immunity, which easily leads to recurrent respiratory infection.

Despite findings showing a close correlation between type II asthma and BAL neutrophilia, our recent studies of asthma demonstrate that there are some type II asthma patients without BAL neutrophilia. Thus, this study was performed to clarify clinical features of type II asthma without BAL neutrophilia (BALn⁻) by comparing features of BALn⁺ patients with same type.

Table 3 shows differences in clinical features between BALn⁺ and BALn⁻ patients with type II asthma. As shown in Table 3, patient age was higher in BALn⁻ patients than in those with BALn⁺. Bronchial hyperresponsiveness in both asthma groups was not different from that in other types of asthma. FEV 1.0% value, the proportion of BAL lymphocytes and serum IgG level were markedly decreased in BALn⁺ patients with type II asthma compared to those in other types of asthma. In contrast, decrease in FEV 1.0% value and serum IgG level were not so remarkable in BALn⁻ patients with same type, and the proportion of BAL lymphocytes showed a tendency to increase, probably due to aging.

These results suggest that severity of asthma is in general more mild in BALn⁻ patients with type II asthma compared to BALn⁺ of same type. Further studies are necessary to analyze the onset mechanisms of BALn⁻ asthma with type II.

Table 3. Comparison in clinical features between BALn⁺ and BALn⁻ patients with type II asthma.

	Type II asthma	
	BALn ⁺	BALn ⁻
Age (years)	50<	60<
Age at onset (years)	40<	35<
Bronchial reactivity	→	→
FEV1.0%	↓↓	↓
BAL lymphocytes	↓↓	↑
Serum IgG	↓↓	↓

BALn⁺; type II asthma with BAL neutrophilia, BALn⁻; type II asthma without BAL neutrophilia, *arrows represent the value compared to healthy subjects.

Conclusion

Type II (bronchiolar obstruction) asthma is closely related to BAL neutrophilia. The present study showed that there are some type II asthma patients without BAL neutrophilia. Clinical features of this type of asthma were studied comparing to same type of asthma with BAL neutrophilia.

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BAL液中好中球増加をともなわないII型喘息について

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細気管支閉塞型 (II型) 喘息の臨床的特徴が, BAL液中の好中球頻度との関連のもとに検討された。対象13例のうち, 7例がBAL液中好中球増加 (平均好中球頻度; 53.5%) をともなう症例 (BALn⁺) で, 残りの6例はBAL液中好中球増加をともなわない (3.5%) 症例 (BALn⁻) であった。1. 平均年齢は, BALn⁺症例 (55.0才) に比べ, BALn⁻症例 (66.0才) でより高い傾向が見ら

れた。2. メサコリンに対する気道過敏性は, BALn⁺症例に比べBALn⁻症例でやや高い傾向が見られたが, 両者間に有意の差は見られなかった。3. FEV1.0%値は, BALn⁻症例に比べBALn⁺症例で有意に低い値を示した ($P<0.05$)。4. BAL液中リンパ球頻度はBALn⁺症例でBALn⁻症例に比べ有意に低い値を示した ($P<0.001$)。5. 血清 IgG, IgAおよび IgM値には両者間に有意の差は見られなかったが, IgG値はBALn⁺症例でより低い傾向が見られた。これらの結果より, II型喘息にはBAL液中好中球増加を示す症例と示さない症例の2種類があること, そして前者は免疫能の低下と, そして後者は加齢とある程度の関連があることが示唆された。

キーワード: 気管支喘息, 細気管支閉塞, BAL好中球, 免疫能低下, 加齢