◎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 FEV1.0% was significantly lower in $BALn^+$ patints than in those with $BALn^-$ ($p<0.01$). 4. The proportion of BAL lymphocytes was signicantly 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 airways [1-5)]. 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 therapy [6-8)].

Airway inflammation, in which migration

of lymphocytes, eosinophils, neutrophils, and basophils into local allergic reaction sites is observed in patients with asthma [9-12]. 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 (clinial 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 $\mu g/ml$) were prepared for bronchial challenge according to the mthod used by Chai et al[19]. The increase of total respiratory resistance (Rrs) after methacholine inhalation was measured by the oscillation method [20]. 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 methud previosly described when they were symptom free [4-7], and informed consent for this examination was obtained from all study subjects.

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

Serum lgE was measured by radioimmunosorbent test (RIST) and lgE 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

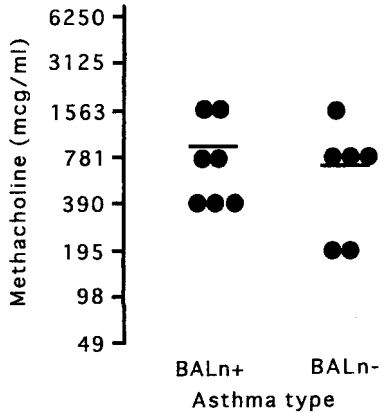

Fig. 1. Bronchial reactivity to methacholine in type II asthma with ($BALn^+$) and without BAL neutrophilia ($BALn^-$)

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%.

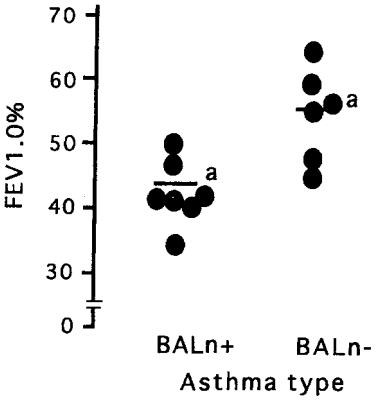

Fig. 2. Comparision in FEV1.0% between type II patients with ($BALn^+$) and without BAL neutrophilia ($BALn^-$). a;$p<0.01$.

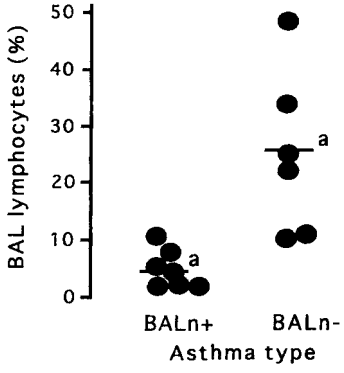

Fig. 3. Comparison in the proportion of BAL lymphocytes between type II patients with ($BALn^+$) and without BAL neutrophilia ($BALn^-$). a;$p<0.001$.

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 type [1-5]. Moreover, type Ia is divided into two subtypes according to expectoration per day. Ia−1(0 −49 mℓ) and Ia−2(50−99mℓ) [5].

Regardig the proportion of inflammatory cells, BAL eosinophilia is often found in type Ib (hypersecretion) [21], 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. Futhermore, 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 diffrences in clinical features between $BALn^+$ and $BALn^-$ patients with type II asthma. As shown in Table 3, patint 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