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Yoshiro Tanizaki, *Okayama University*
Hikaru Kitani, *Okayama University*
Morihiro Okazaki, *Okayama University*
Takashi Mifune, *Okayama University*
Fumihiro Mitsunobu, *Okayama University*
Masakuni Tanimizu, *Okayama University*
Naoko Honke, *Okayama University*
Yasuharu Kusaura, *Okayama University*
Koji Ochi, *Okayama University*
Hideo Harada, *Okayama University*
Ryo Soda, *Okayama University*
Kiyoshi Takahashi, *Okayama University*
Ikuro Kimura, *Okayama University*

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Abstract

Twenty-one patients with atopic asthma were classified into three types according to their symptoms (clinical diagnosis): Ia, simple bronchoconstriction; Ib, bronchoconstriction + hypersecretion; and II, bronchiolar obstruction, and this classification was compared with a classification made according to clinical findings and examinations (score diagnosis). Type Ib asthma was characterized by the increased incidence of eosinophils in bronchoalveolar lavage fluid (BALF), while type II was characterized by ventilatory dysfunction in small airways and the increased incidence of neutrophils in BALF. Four patients, whose expectoration was between 50 and 99ml/day, of the 12 with type Ia assessed by clinical diagnosis were evaluated as type Ib by score diagnosis. One patient with type II by clinical diagnosis was assessed as questionable type II by score diagnosis. In the other 16 patients, the clinical and score diagnoses were the same.

KEYWORDS: bronchial asthma, classification, ventilatory function, cellular composition of BALF, sore diagnosis

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Asthma Classification by a Score Calculated from Clinical Findings and Examinations in Subjects Sensitive to Inhalant Allergens

Yoshiro Tanizaki*, Hikaru Kitani, Morihiro Okazaki, Takashi Mifune, Fumihiro Mitsunobu, Masakuni Tanimizu, Naoko Honke, Yasuharu Kusaura, Koji Ochi[a], Hideo Harada[a], Ryo Soda[b], Kiyoshi Takahashi[b] and Ikuro Kimura[b]

Division of Medicine, Misasa Medical Branch, Okayama University Medical School, Misasa, Tottori 682-01, Japan, [a]Department of Laboratory Medicine and [b]Second Department of Medicine, Okayama University Medical School, Okayama 700, Japan

Twenty-one patients with atopic asthma were classified into three types according to their symptoms (clinical diagnosis): Ia, simple bronchoconstriction; Ib, bronchoconstriction + hypersecretion; and II, bronchiolar obstruction, and this classification was compared with a classification made according to clinical findings and examinations (score diagnosis). Type Ib asthma was characterized by the increased incidence of eosinophils in bronchoalveolar lavage fluid (BALF), while type II was characterized by ventilatory dysfunstion in small airways and the increased incidence of neutrophils in BALF. Four patients, whose expectoration was between 50 and 99ml/day, of the 12 with type Ia assessed by clinical diagnosis were evaluated as type Ib by score diagnosis. One patient with type II by clinical diagnosis was assessed as questionable type II by score diagnosis. In the other 16 patients, the clinical and score diagnoses were the same.

Key words : **bronchial asthma, classification, ventilatory function, cellular composition of BALF, score diagnosis**

Asthma classification in Japan has generally been carried out in accordance with the criteria described by Swineford (1). These criteria, however, are sometimes complicated and unsuitable for clinical application, since the criteria of mixed type and infectious type are unclear, and are not related to medication and bronchial asthma prognosis. Asthma has also been classified into two types, extrinsic and intrinsic, or atopic and non-atopic, on the basis of the presence or absence of an elevated serum concentration of IgE (2). Although it has been suggested that asthma is a disease induced by IgE-mediated reactions (3, 4), it is difficult for physicians to evaluate the presence or absence of IgE-mediated allergy in some cases of asthma in adults, since there is no agreement about the level of serum IgE that

* To whom correspondence should be addressed.

Abbreviations used: $FEV_{1.0\%}$, forced expiratory volume in one second; % MMF, % maximal mid-expiratory flow rate; $\%\dot{V}_{50}$, % maximal flow rate at 50 % of vital capacity; $\%\dot{V}_{25}$, % Maximal flow rate at 25 % of vital capacity.

exceeds the normal limit.

Bronchial asthma is characterized by transient wheezing and dyspnea. The symptoms of asthma are primarily elicited by bronchoconstriction and are accompanied by hypersecretion and edema of the mucous membranes. In addition to these pathophysiological changes, some asthmatics show bronchiolar obstruction during their attacks. We have previously attempted to classify bronchial asthma into three types according to the clinical symptoms caused by the pathophysiological changes; bronchoconstriction, hypersecretion, and bronchiolar obstruction (5-9).

In the present study, patients with bronchial asthma were clinically classified into three types according to their symptoms, and the classification was assessed by a score calculated from clinical findings and examinations.

Subjects and Methods

The subjects were 21 atopic asthmatics who were sensitive to one or more of various inhalant allergens. They were all admitted to Misasa Branch Hospital for periods of more than 2 weeks because of the severity of their symptoms. All of them were non-smokers; their mean age was 44.3 years, with a range of 21 to 65 years. The serum IgE levels of these subjects ranged from 65 to 2439 IU/ml (mean; 514 IU/ml).

The subjects were clinically observed for more than one year, and observations of their severe asthma attacks were made for more than one week. Clinical findings and signs including auscultation findings, amount of expectoration per day and degree of severity of asthma attacks were recorded every day during their hospitalization. The amounts of expectoration per day were expressed as a mean for three days during asthma attacks.

Classification of asthma by clinical symptoms and signs (clinical diagnosis) was performed according to criteria described previously (5-9). These criteria were:

Type Ia. Simple bronchoconstriction type: patients with symptoms such as wheezing and dyspnea, which are elicited mainly by bronchoconstriction.

Type Ib. Bronchoconstriction + hypersecretion type: patients with symptoms due to hypersecretion (more than 100 ml/day of expectoration), in addition to bronchoconstriction.

Typy II. Bronchiolar obstruction type: patients with symptoms elicited mainly by bronchiolar obstruction.

In the diagnosis of each asthma type, type Ia was assessed to the fundamental type. When hypersecretion or bronchiolar obstruction was present in addition to the symptoms of type Ia, the patients were evaluated as type Ib or type II. Patients with both hypersecretion and bronchiolar obstruction were diagnosed as type II.

The subjects were also classified by a score calculated from their findings and examinations (score diagnosis). The score diagnosis was performed by allocating 1 to 5 points to symptoms and laboratory findings as shown in Table 1. A patient with a score of 0 to 4 points was diagnosed as type Ia, a score of 5 to 11 points was type Ib, and a score of 12 points or more was type II (Table 1).

Bronchoalveolar lavage (BAL) was carried out in all subjects (except one patient who had an anaphylactic reaction to the lidocaine used for local anesthesia) by means of a bronchofiberscope (Olympus BF-1T) when the subjects were symptom-free (9-11). Informed consent for the BAL examination was obtained from all subjects. After the bronchofiberscope was routinely wedged in a segment of the right middle lobe, 4×50 ml aliquots of sterile isotonic saline at 37°C were introduced into the segment, and were immediately aspirated into

Table 1 Allocation of scores to symptoms and laboratory findings for classification of asthma types

Symptoms and laboratory findings	Score(s) (point)
1. Expectoration more than 100 ml a day[a]	5
2. Expectoration between 50 and 99 ml a day	4
3. Presence of sputum in several areas of the airways on auscultation	1
4. Day-long difficulty of expectoration	1
5. Transient bubbling rales in both lower lung fields on auscultation	4
6. Alveolar breath sounds in both lower lung fields markedly decreased or disappeared on auscultation	4
7. Value of $\%V_{25}$ less than 10 %	4
8. Frequency of neutrophils in BALF more than 20 %	4

a Mean for three days during asthma attacks. All of the clinical findings and signs described above should be observed for more than three days during asthma attacks.

Classification score: from 0 to 4 points: type Ia, from 5 to 11 points: type Ib, 12 points or more: type II

siliconized glassware. After filtration through a sterile steel mesh, a total cell count was performed. The aspirate was centrifuged at 1,200 rpm for 10 min at 4°C, and the resultant cell pellet was resuspended in Tris ACM. Smear preparations were made with the cell suspension. After being air-dried, the slides were stained with May Giemsa. A differential cell count was performed on 500 cells excluding epithelial cells. In this study, the mean recovery rate was 26.6 ± 10.7% (± SD). The number of cells aspirated into BAL fluid was $9.58 \pm 10.2 \times 10^6$. The results were expressed as a percentage of the total number of cells.

Ventilatory function was measured in all subjects during an attack-free period by a Box Spiror 81 (Chest Co.).

Specific IgE antibodies for an allergen were measured by a radioallergosorbent test (RAST). The RAST score was graded from 0+ to 5+, and a patient with a score of 2+ or more was evaluated as being sensitized by the allergen. Serum levels of total IgE were estimated by a radioimmunosorbent test (RIST).

Results

Asthma Classification by Clinical Diagnosis

The subjects were classified by clinical diagnosis according to their symptoms. Twelve subjects were diagnosed as type Ia, 3 as type Ib, and 6 as type II. In 4 of the 12 subjects diagnosed as type Ia, the amount of expectoration was between 50 and 99 ml/day. Mean patient ages were 37.5 years for type Ia, 44.3 years for type Ib and 57.8 yesrs for type II.

Asthma Classification by Score Diagnosis

Type Ia asthma. Table 2 shows the clinical data of patients with type Ia by clinical diagnosis. Ten patients were sensitive to the house dust mite. The amount of expectoration was less than 50 ml/day in 8 patients (group A) and 50 ml or more in 4 patients (group B). The mean $FEV_{1.0\%}$ value was 74.7 ± 11.0% and the mean $\%\dot{V}_{25}$ value was 35.1 ± 17.4%. The $FEV_{1.0\%}$ and $\%\dot{V}_{25}$ values in groups A and B were not significantly different. The incidence of neutrophils in BALF was from 0.3% to 8.2% in all subjects with type Ia, and no significant difference was found between groups A and B. The mean incidence of eosinophils in BALF was 3.5 ± 1.2% in the 8 group A patients and 40.8 ± 24.4% in the 4 group B patients. There was a significant difference between groups A and B ($p < 0.001$) in the incidence of eosinophils. The patients of group A scored from 0 to 2 points, and were diagnosed as type Ia by score diagnosis. The patients of group B scored from 5 to 6

Table 2 Clinical findings and examinations of subjects with type Ia classified by symptoms and signs (clinical diagnosis)

Case	Sex	Age	IgE (IU/ml)	RAST score	Expect* (ml/day)	$FEV_{1.0\%}$	$\%\dot{V}_{25}$	BALF (%)	
								Neut.	Eos.
1. AI	F	23	87	HD2+	67	69.0	13.0	2.6	12.3
2. MY	F	31	808	Ca2+	58	86.7	48.5	0.5	46.0
3. MK	M	50	519	BW2+	57	62.3	14.8	0.3	26.5
4. TK	M	47	1754	HD2+	55	87.7	67.0	2.4	77.8
5. KF	M	41	170	HD2+	40	68.4	29.2	1.4	4.0
6. KH	F	57	199	HD2+	27	63.9	25.3	6.4	5.1
7. MY	F	36	170	HD2+	13	70.2	17.5	1.4	4.0
8. HM	F	49	260	HD2+	12	79.3	46.3	1.4	3.4
9. TS	M	21	283	HD2+	10	89.8	64.9	8.2	1.2
10. EY	F	47	1003	HD2+	10	62.5	27.4	1.0	3.0
11. MI	M	24	100	HD2+	5	77.6	36.2	0.4	2.2
12. MI	M	24	123	HD2+	5	70.0	30.9	0.8	4.8

* Amount of expectoration per day is expressed as the mean for three days during asthma attacks. Expect, expectoration; HD, house dust; Ca, *Candida albicans*; BW, buckwheat; Neut, neutrophils; Eos, eosinophils.

RAST, radioallergosorbent test; BALF, bronchoalveolar lavage fluid, $FEV_{1.0\%}$, $\%\dot{V}_{25}$, See footnote.

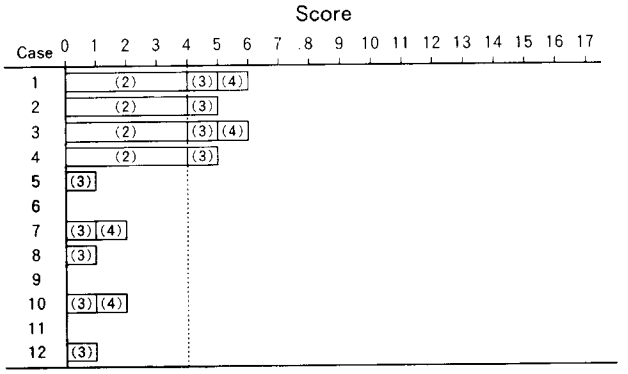

Fig. 1 Score for asthma classification (score diagnosis) in patients with type Ia evaluated by clinical symptoms and signs (clinical diagnosis). Numbers in parenthesis represent the numbers shown in Table 1.

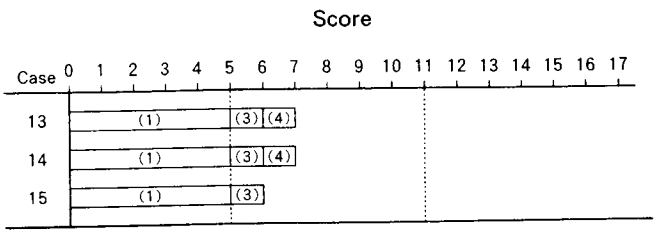

Fig. 2 Score for asthma classification (score diagnosis) in patients with type Ib evaluated by clinical symptoms and signs (clinical diagnosis). Numbers in parentheses represent the number shown in Table 1.

Table 3 Clinical findings and examinations of subjects with type Ib classified by symptoms and signs (clinical diagnosis)

Case	Sex	Age	IgE (IU/ml)	RAST score	Expect* (ml/day)	$FEV_{1.0\%}$	$\%\dot{V}_{25}$	BALF (%)	
								Neut.	Eos.
13. YM	F	54	87	GP2+	303	65.3	36.1	4.8	28.6
14. SS	F	39	2439	Ca2+	167	63.1	35.7	0.6	36.9
15. HY	F	40	412	HD2+	167	65.3	22.2	—	—

* Amount of expectoration per day is expressed as the mean for three days during asthma attacks. GP, grass pollen; Other abbreviations; See Table 2.

points, and were evaluated as type Ib by score diagnosis (Table 2, Fig. 1)

Type Ib asthma. The results of the clinical findings and examinations in patients with type Ib assessed by clinical diagnosis are shown in Table 3. All patients had expectoration of more than 100 ml/day. The mean $FEV_{1.0\%}$ value was $64.6 \pm 21.0\%$ and the mean $\%\dot{V}_{25}$ value was $31.3 \pm 6.5\%$. The $FEV_{1.0\%}$ value in type Ib patients was lower than that in type Ia assessed by clinical diagnosis, although the difference between them was not significant. The incidence of neutrophils in BALF was less than 10%, with a mean of 2.7%, while the frequency of eosinophils in BALF was markedly increased with a mean of 32.8%. The score of these patients was from 6 to 7 points, all of them being assessed as type Ib by score diagnosis (Table 3, Fig. 2).

Type II asthma. Six patients were assessd as type II by clinical diagnosis. All subjects were sensitive to the house dust mite. The characteris-

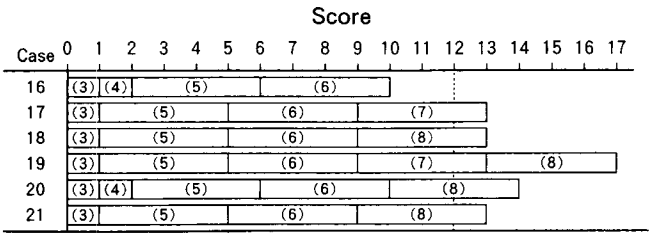

Fig. 3 Score for asthma classification (score diagnosis) in patients with type II evaluated by clinical symptoms and signs (clinical diagnosis). Numbers in parenthesis represent the numbers shown in Table 1.

Table 4 Clinical findings and examinations of subjects with type II classified by symptoms and signs (clinical diagnosis)

Case	Sex	Age	IgE (IU/ml)	RAST score	Expect* (ml/day)	$FEV_{1.0\%}$	$\%\dot{V}_{25}$	BALF (%)	
								Neut.	Eos.
16. MI	M	41	217	HD2+	42	62.5	12.4	11.7	2.7
17. KS	F	64	320	HD2+	38	76.0	9.5	15.0	21.0
18. SF	M	63	260	HD2+	35	63.4	11.5	51.5	40.5
19. KF	M	58	1260	HD2+	32	58.8	8.6	37.5	8.4
20. KS	F	65	65	HD2+	5	58.8	17.7	56.2	0.2
21. HO	M	66	253	HD2+	5	53.2	12.3	76.3	0.4

* Amount of expectoration per day is expressed as the mean for three days during asthma attacks. Abbreviations; See Table 2.

tics of these patients are summarized in Table 4. The amount of expectoration was less than 50 ml/day. The mean $FEV_{1.0\%}$ value was $62.1 \pm 7.0\%$. The mean $\%\dot{V}_{25}$ value was $12.0 \pm 2.9\%$, and values less than 10 % were found in 2 of these 6 patients. Mean $FEV_{1.0\%}$ value in type II patients was significantly lower than that in type Ia ($p < 0.05$). Furthermore, the mean $\%\dot{V}_{25}$ value in type II was significantly lower than in type Ia ($p < 0.01$) and in type Ib ($p < 0.001$). The incidence of neutrophils in BALF was remarkably increased: more than 20 % in 4 of these 6 patients. The incidence of neutrophils in type II patients ($41.4 \pm 22.9\%$) was signficantly higher than that in type Ia ($p < 0.001$), while the incidence of eosinophils in BALF in these patients ranged from 0.2 % to 40.5 %. The score was more than 12 points in 5 patients, who were evaluated as type II by score diagnosis, while the score in one patient was 10 points; this patient was evaluated as questionable type II (Table 4, Fig. 3).

Discussion

The main symptoms of bronchial asthma are wheezing and dyspnea. However, symptoms among asthma patients are not uniform. These variations are largely attributed to the various pathophysiological changes, *i.e.*, bronchoconstriction, hypersecretion and bronchiolar obstruction, that take place in the airways. Many asthma patients show typical asthma symptoms, *i.e.*, marked wheezing and dyspnea with prolonged expiration, while some patients have large amounts of expectoration in addition to the asthma symptoms. Other patients show slight or no wheezing in spite of marked dyspnea.

Our previous studies have shown that bron-

chial asthma can be divided into three types according to clinical symptoms and signs (5-9). The characteristics of each asthma type determined by clinical diagnosis have been studied by ventilatory function tests (12), determination of cellular composition in BALF (8,9), and assessment of prognosis (13).

In ventilatory function tests in type II asthmatics, dysfunction was found to be more predominant in the ventilation of small airways, shown by parameters such as %MMF, $\%\dot{V}_{25}$ and $\%\dot{V}_{25}$, than in the ventilation of large airways, shown by parameters such as $FEV_{1.0\%}$ and %PEFR (9). In the current study, $FEV_{1.0\%}$ and $\%\dot{V}_{25}$ values were compared in clinical asthma types classified by clinical and score diagnoses. A marked decrease in $\%\dot{V}_{25}$ was observed in type II patients, showing this to be one of the characteristics of type II patients with bronchiolar obstruction. Airway inflammation has become widely accepted as a common feature of asthma (14-16) and blood cells such as lymphocytes, neutrophils, eosinophils and basophils have been identified as inflammatory cells (17-23). In this study, analysis of the cellular composition in the BALF of asthmatics showed an increased incidence of neutrophils in BALF in type II asthmatics and an increased number of eosinophils in type Ib. These increases were associated with hypersecretion (4, 8, 24). The results obtained here showed that the incidence of BAL neutrophils was significantly higher in type II patients than in type Ia and Ib patients, and that the incidence of eosinophils in BALF was increased in group B (expectoration; 50-99 ml/day) of type Ia, and in type Ib, as classified by clinical diagnosis. These findings and examinations demonstrate that the characteristics of type II asthma are ventilatory dysfunction in small airways, expressed by $\%\dot{V}_{25}$, and an increased incidence of neutrophis in BALF.

The subjects with each asthma type assessed by clinial diagnosis have symptoms and signs that are peculiar to each type. Thus, bronchial asthma can be divided into three types according to these clinical symptoms and signs. The data in this study clearly indicate that the characteristics of each asthma type can be demonstrated by such examinations as ventilatory function and the cellular composition of BALF.

Regarding the comparison between clinical and score diagnoses for asthma classification, 4 patients (group B) (whose expectoration was between 50 and 99 ml/day) of the 12 patients evaluated as type Ia by clinical diagnosis were classified as type Ib by score diagnosis. All type Ia patients who were evaluated as type Ib by score diagnosis were suspected to have pathophysiological changes that were similar to those in type Ib with regard to an increased incidence of eosinophils in BALF. One patient classified as type II by clinical diagnosis could not be evaluated as type II by score diagnosis, since the score was less than 12 points. This patient was thus assessed as questionable type II by score diagnosis.

In this study, asthma classification by clinical symptoms was compared with the classification by clinical findings and examinations (score diagnosis). It may be concluded from the results that asthma classification should be initially assigned according to clinical symptoms, and later, if possible, asthma types should be assessed by score diagnosis.

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