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Abstract

The correlation between blood eosinophilia and anti-IgE-mediated histamine release was investigated in 22 bronchial asthma patients with peripheral eosinophilia (over 8%). In the cases (Group A-1 and Group A-2) in which house dust was the specific antigen, significant histamine release from basophils was induced by anti-IgE and house dust. The result indicates a relationship between eosinophilia and the IgE-mediated mechanism of disease onset. In the cases (Group A-3) with RAST scores of 0+ and 1+ to house dust, the anti-IgE-induced histamine release varied from low to high percentages, and the participation of the IgE-mediated pathway was indicated in some cases. In the cases (Group B) with negative skin reactions, few patients had a family history of allergic disease. Their ages at onset were higher, and they demonstrated lower total IgE levels. These cases showed an extremely low percent of histamine release from basophils, which indicated the absence of a correlation between eosinophilia and IgE-mediated mechanisms.

KEYWORDS: blood eosinophilia, histamine release, IgE-mediated reaction, asthma

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BLOOD EOSINOPHILIA IN BRONCHIAL ASTHMA AND ITS RELATIONSHIP TO IgE-MEDIATED REACTIONS

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Abstract. The correlation between blood eosinophilia and anti-IgE-mediated histamine release was investigated in 22 bronchial asthma patients with peripheral eosinophilia (over 8%). In the cases (Group A-1 and Group A-2) in which house dust was the specific antigen, significant histamine release from basophils was induced by anti-IgE and house dust. The result indicates a relationship between eosinophilia and the IgE-mediated mechanism of disease onset. In the cases (Group A-3) with RAST scores of 0+ and 1+ to house dust, the anti-IgE-induced histamine release varied from low to high percentages, and the participation of the IgE-mediated pathway was indicated in some cases. In the cases (Group B) with negative skin reactions, few patients had a family history of allergic disease. Their ages at onset were higher, and they demonstrated lower total IgE levels. These cases showed an extremely low percent of histamine release from basophils, which indicated the absence of a correlation between eosinophilia and IgE-mediated mechanisms.

Key words : blood eosinophilia, histamine release, IgE-mediated reaction, asthma.

It has been reported that the onset of bronchial asthma is mainly mediated by IgE, mast cells, basophils and eosinophils (1, 2). In the onset mechanism, the antigen-antibody reaction causes release of histamine, SRS-A and ECF-A from mast cells and basophils (3). ECF-A is known to attract eosinophils to allergic reaction sites, but mechanisms causing blood eosinophilia are not known. Marked eosinophilia is observed in atopic asthma in which the IgE-mediated immediate reaction is primarily involved.

This study was designed to investigate the participation of eosinophils in bronchial asthma, particularly in terms of IgE antibody-mediated reactions.

MATERIALS AND METHODS

Subjects. Twenty-two patients with bronchial asthma, 15 females and 7 males, were involved in this study. They were selected for the study because they fulfilled the following criteria: 1) the maximum percent eosinophil count of the patients in one recent year was 8% or higher, and 2) the patients had a positive skin reaction to house dust or negative skin reac-

tion to various allergen extracts. Their ages averaged 39.6 years, and ranged from 16 to 71 years. The average age at onset of the disease was 29.8 years (4-62 years), and their mean total serum IgE was 495 IU/ml (55-1910). A family history of allergic diseases was observed in 8 cases (36.4%).

Classification of Subjects. The patients were separated into 2 groups according to the skin reaction to allergen extract: Group A demonstrated a positive skin reaction to house dust, and Group B showed a negative skin reaction to various allergen extracts. Group A was further classified into Group A-1, A-2 and A-3 according to the total serum IgE levels and the RAST score to house dust. In Group A-1, the total serum IgE levels were over 501 IU/ml and RAST scores were 2+ or higher. Patient in Group A-2 had total serum IgE levels of less than 500 IU/ml and RAST scores of 2+ or higher. Patients in Group A-3 had serum IgE levels of less than 500 IU/ml and RAST scores of 0+ and 1+. Comparative assessments were performed on these 3 subgroups (Table 1).

T TABLE 1. CLASSIFICATION OF ASTHMATIC SUBJECTS BY SERUM IGE, SKIN REACTION AND RAST

Group	Serum IgE (IU/ml)	Skin test to HD	RAST score to HD
A-1	501 - ↑	+	2+ - ↑
A-2	0 - 500	+	2+ - ↑
A-3	0 - 500	+	0 - 1+
B	0 - 500	-	NT

HD; house dust, NT: not tested

Histamine Release from Basophils. Histamine release from basophils was determined by the whole blood method (4), a previously described (5). To 4 ml of heparinized venous blood in a silicon-coated test tube, 0.2 ml of either anti-IgE (10^1 - 10^5 fold dilution) (Hoechst) or house dust (10^2 - 10^6 fold dilution) was added and the mixture was then incubated at 37 °C for 15 min. Histamine release was determined by an automated histamine analysis system (Technicon) (6). Administration of all drugs was suspended for 12 h before blood sampling for the assessment of histamine release.

Total serum IgE and specific IgE antibodies. The serum IgE levels and the specific IgE to house dust were determined by the RIST method and RAST method (Pharmacia).

RESULTS

Characteristics of subjects. Characteristics of the subjects are summarized in Table 2-A. The average age was highest in Group B, and the age at onset was also highest in that group (41.1 years old), while the age at onset in Group A was under 40 years. A family history of allergic disease was observed in 3 out of 6 cases in Group A-1 and in 3 out of 3 cases in Group A-2, indicating a high incidence in these groups. Group A-3 and Group B, by contrast, had lower incidences: 1 out of 6 cases in Group A-3, and 1 out of 7 cases in Group B (Table 2-A).

Correlation between total serum IgE levels and blood eosinophilia. The total serum IgE levels were 1306 ± 168 IU/ml (mean \pm SEM) in Group A-1, 263 ± 28 IU/ml in Group A-2, 199 ± 31 IU/ml in Group A-3 and 153 ± 28 IU/ml in Group B. The

mean total serum IgE levels in Group A-3 and B were lower than 200 IU/ml. The peripheral eosinophil counts were 11 ± 1.2 % in Group A-1, 9 ± 1.3 % in Group A-2, 13 ± 3.0 % in Group A-3 and 17 ± 2.2 % in Group B. Group B exhibited the highest peripheral eosinophil count despite the fact that it had the lowest total IgE level (Table 2-B).

TABLE 2-A. CHARACTERISTICS OF ASTHMATIC SUBJECTS GROUP CLASSIFIED BY SKIN REACTION, SERUM IgE AND RAST

Group	No of cases	Age	Age of onset	F.H.	Skin test			RAST score to H.D.
					H.D.	Rag.	Ca.	
A-1	6	34.8* (22-44)	27.6 (6-44)	3/6	6/6	3/6	5/6	6/6
A-2	3	27.0 (16-39)	5.3 (4-6)	3/3	3/3	1/3	2/3	3/3
A-3	6	40.3 (21-71)	31.2 (4-68)	1/6	6/6	1/6	1/6	0/6
B	7	48.4 (21-70)	41.1 (11-58)	1/7	0/7	0/7	0/7	0/7

F.H.; family history with allergic diseases. H.D.; house dust. Rag; ragweed. Ca; candida. Numbers in parentheses represent range. *Mean

TABLE 2-B. TOTAL SERUM IgE AND BLOOD EOSINOPHILS IN GROUP A-1, A-2, A-3 AND B.

Group	No of cases	Serum IgE (IU/ml)		Blood eosinophils (%)	
		Mean \pm SE	Range	Mean \pm SE	Range
A-1	6	1306 \pm 168	809-1910	11 \pm 1.2	8-16
A-2	3	263 \pm 28	217-315	9 \pm 1.3	8-12
A-3	6	199 \pm 31	64-274	13 \pm 3.0	9-28
B	7	153 \pm 28	55-284	17 \pm 2.2	8-23

Maximum percent histamine release in each group. The maximum percent histamine release induced by anti-IgE accounted for 54.4 ± 5.9 % in Group A-1, 36.5 ± 6.2 % in Group A-2, 22.1 ± 3.0 % in Group A-3 and 12.8 ± 2.2 % in Group B. The percent release in Group B was significantly lower than the release in Group A-1 and Group A-2 ($p < 0.001$). The maximum percent histamine release in Group A-3 was between that of Group A-2 and Group B. Slight or moderate histamine release induced by anti-IgE was observed in Group A-3. The percent of spontaneous histamine release in all the subjects was 3.9 ± 0.5 % (Fig. 1).

Dose-response curve of histamine release induced by anti-IgE. According to the dose-response curve illustrated in Fig. 2, the percent histamine release induced by anti-IgE in Group A-1 increased in proportion to the elevation of anti-IgE concentration. The percent histamine release in Group A-2 reached the highest level with the

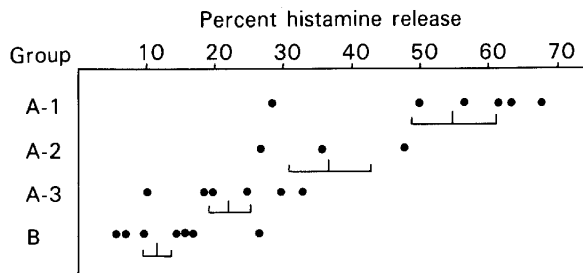


Fig. 1. Maximum percent histamine release from basophils induced by anti-IgE in Groups A-1, A-2, A-3 and B.

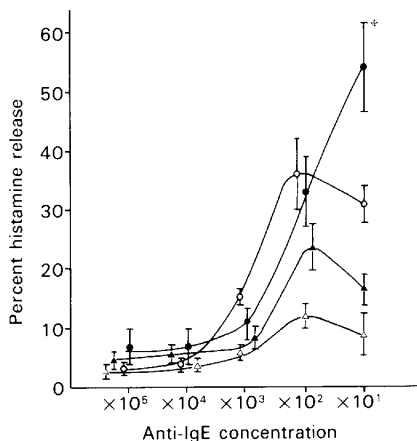


Fig. 2. Dose-response curve of anti-IgE-induced histamine release from basophils in Group A-1 (●—●), A-2 (○—○), A-3 (▲—▲) and B (△—△). * mean \pm SEM.

anti-IgE concentration of $\times 10^2$, but a decreasing trend was observed with a concentration of $\times 10^1$. The dose-response curves of Group A-3 and Group B showed similar trends to the curve of Group A-2. However, Group B exhibited the lowest percent of histamine release, indicating that peripheral basophils responded only slightly to anti-IgE in Group B (Fig. 2).

Dose-response curve of histamine release induced by house dust. Dose-response curves of histamine release induced by house dust were examined in patients in Group A who showed a positive skin reaction to house dust. The dose-response curves of Group A-1 showed that the increase in percent histamine release paralleled the elevation of house dust concentrations. Group A-2 showed curves similar to those of Group A-1. It was clear from these results that reactions between specific antigen and IgE antibodies on basophils caused significant histamine release in these cases. On the other hand, no significant histamine release was induced by house dust in Group A-3 (Fig. 3).

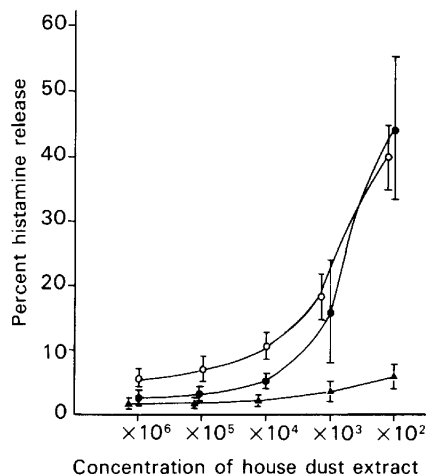


Fig. 3. Dose-response curve of house dust extract-induced histamine release from basophils in Group A-1 (●—●), A-2 (○—○), A-3 (▲—▲). * mean \pm SEM.

DISCUSSION

It is well known that peripheral eosinophilia is observed in allergic diseases like bronchial asthma. We have investigated the correlation between blood basophils and eosinophilia in peripheral blood and sputum from patients with bronchial asthma (7, 8). Our previous results showed that eosinophilia is accompanied with blood basophilia in the pre-attack stage of bronchial asthma and the responsiveness of basophils to anti-IgE markedly varies according to individual patients (9). The basophil-related eosinophilia is often observed in the IgE-mediated immediate allergic reaction associated with a series of onset mechanisms such as those involving IgE, mast cells, basophils and eosinophils. This kind of eosinophilia is clinically observed in atopic bronchial asthma. However, mechanisms as yet unknown in addition to the IgE-mediated pathway may participate in causing eosinophilia in bronchial asthma (10). In the present study, the eosinophilia in bronchial asthma was investigated in relation to the IgE-associated pathway for onset. The results revealed that Group A-1 and Group A-2 patients with atopic characteristics frequently had a family history of allergic disease and significantly higher histamine release induced by anti-IgE and house dust. Furthermore, the patients in these groups had relatively lower ages of onset. It was proved that a histamine releasing mechanism mediated by not only anti-IgE but also house dust participated in the allergic reactions of these patients. On the other hand, Group B patient demonstrated a higher mean eosinophil count than those in the other groups. They had higher ages at onset (average age: over 40 years), lower total serum IgE levels and markedly lower anti-IgE-induced percent histamine release from basophils. These findings strongly suggest the absence of histamine release mechanisms mediated by IgE receptors on basophils. In Group A-3 patients, who had a

positive skin reaction to house dust and RAST scores of 0+ and 1+, house dust-induced histamine release from basophils was not observed, but the reactivity of basophils to anti-IgE varied markedly among individual cases. The eosinophilia in some patients of Group A-3 was ascribable to IgE-associated reactions. It is suggested that in patients with low serum IgE levels, significant histamine release from basophils is caused by anti-IgE. Our findings revealed that eosinophilia in bronchial asthma was caused by either the IgE-mediated pathway or other mechanisms unrelated to IgE (Table 3).

TABLE 3. PARAMETERS OF IGE-MEDIATED REACTIONS IN BRONCHIAL ASTHMA WITH BLOOD EOSINOPHILIA

Group	Elevation serum IgE	Specific IgE	Skin test to HD	HR by anti-IgE
A-1	+	+	+	+
A-2	-	+	+	+
A-3	-	-	+	- ~ +
B	-	-	-	-

HD; house dust, HR; histamine release

In the IgE-mediated pathway, stimulation by specific antigen or by anti-IgE induces bridging of IgE receptors on mast cells or basophils, and releases chemical mediators such as histamine and SRS-A (1, 2). Consequently, histamine or SRS-A releasing mechanisms mediated by IgE receptors must play important roles in this pathway for the onset of bronchial asthma. Basophils in patients with bronchial asthma generally release histamine easily (11), and the specific antigen-induced histamine release correlates well with clinical symptoms (12, 13) and skin reactions (14). Due to high reactivity of IgE receptors, significant release of histamine from basophils was induced by anti-IgE in all the asthma cases, and no significant differences according to types of allergies were found (15). However, our study clearly showed that anti-IgE induced histamine release from basophils was markedly affected by the type of bronchial asthma. Eosinophilia in bronchial asthma might be caused either by IgE-mediated mechanisms or by other mechanisms unrelated to IgE. The details of the latter mechanisms remain to be clarified in future.

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