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Cell-mediated immunity in bronchial asthma evaluated by purified protein derivative- and *Candida albicans*-skin reaction.

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Abstract

Cell-mediated immunity was examined in 45 patients with bronchial asthma by observing the delayed cutaneous reaction to purified protein derivative (PPD) and *Candida albicans* (*C. albicans*). The delayed skin reaction to PPD showed a decrease with age starting between 50 and 59 years old. The delayed reaction to PPD decreased more prominently with aging, being significantly depressed in the patients aged over 70 years than in those aged between 30 and 49 years (induration, $p < 0.02$; flare, $p < 0.01$). The *C. albicans*-induced skin reaction was significantly lower in the patients aged over 70 years than in those between 60 and 69 years old (induration, $p < 0.01$; flare, $p < 0.05$). The delayed skin reaction to PPD and *C. albicans* was significantly depressed in the patients with a serum IgE level over 1001 IU/ml. Delayed skin reaction to PPD and *C. albicans* was more depressed with aging and an elevated serum IgE, and the age (50-59 years) at the initiation of depression in the PPD-induced delayed skin reaction was younger than that (over 70 years) in the *C. albicans*-induced reaction.

KEYWORDS: cell-mediated immunity, PPD, *Candida albicans*, bronchial asthma

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Cell-Mediated Immunity in Bronchial Asthma Evaluated by Purified Protein Derivative- and *Candida albicans*-Skin Reaction

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Cell-mediated immunity was examined in 45 patients with bronchial asthma by observing the delayed cutaneous reaction to purified protein derivative (PPD) and *Candida albicans* (*C. albicans*). The delayed skin reaction to PPD showed a decrease with age starting between 50 and 59 years old. The delayed reaction to PPD decreased more prominently with aging, being significantly depressed in the patients aged over 70 years than in those aged between 30 and 49 years (induration, $p < 0.02$; flare, $p < 0.01$). The *C. albicans*-induced skin reaction was significantly lower in the patients aged over 70 years than in those between 60 and 69 years old (induration, $p < 0.01$; flare, $p < 0.05$). The delayed skin reaction to PPD and *C. albicans* was significantly depressed in the patients with a serum IgE level over 1001 IU/ml. Delayed skin reaction to PPD and *C. albicans* was more depressed with aging and an elevated serum IgE, and the age (50-59 years) at the initiation of depression in the PPD-induced delayed skin reaction was younger than that (over 70 years) in the *C. albicans*-induced reaction.

Key words : cell-mediated immunity, PPD, *Candida albicans*, bronchial asthma

Humoral immunity, particularly the IgE-mediated immediate immune response plays an important role in the onset of bronchial asthma (1, 2). Chemical mediators released from tissue mast cells and blood basophils, which are the target cells of IgE, act to initiate an immediate allergic reaction (3-7). Another immunoglobulin, IgG and specifically IgG₄, is considered to participate in the immediate allergic reaction (8-10). The role of IgG₄ in the immediate allergic reaction has been reported to be both anaphylactic and prophylactic (11-13).

In spite of a number of studies on humoral immunity in bronchial asthma, there are only a few reports about cell-mediated immunity in the disease (14, 15). It has been reported that in some selected atopics, cell-mediated immune responses which play the major role in defense against *Candida albicans* (*C. albicans*) are suppressed (14-16). The enhancement of cell-mediated immunity has

been suggested to be the pathogenesis of corticosteroid dependent intractable asthma by Kimura *et al.* (17). In the present study, delayed cutaneous hypersensitivity to PPD (purified protein derivative; Seibert's tuberculin) and *C. albicans* was examined in patients with bronchial asthma.

Subjects and Methods

The subjects were 45 patients with bronchial asthma (33 women and 12 men), aged between 23 and 82 years with a mean age of 53.3 years. The subjects were divided into five age groups; 0-29, 30-49, 50-59, 60-69 and over 70 years. The mean level of serum IgE was 481 IU/ml (range, 19-2007 IU/ml). The subjects were also divided into five groups according to serum IgE level: 0 to 100, 101 to 300, 301 to 500, 501 to 1000 and over 1001.

The intradermal skin test was performed with 0.02 ml of commercial *Candida* allergen extract (Torii Pharmaceutical Co.) and 0.1 ml of PPD (Japan BCC Co.). The diameters of induration

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and flare at 48h were measured in mm. The results were expressed as a mean of the two different diameters of induration and flare reactions.

Serum IgE levels were measured by a radioimmunosorbent test (RIST).

Results

Delayed skin reaction to PPD. The mean diameter of induration by PPD was 5.9 ± 3.3 mm in the patients under 29 years old, and the largest (10.9 ± 8.6 mm) in those between the age of 30 and 49 years. The diameter of induration began to decrease in the patients over 50 years old. The mean diameter of induration in the patients between 30 and 49 years old was significantly larger than that in those between 60 and 69 ($p < 0.05$) and over 70 ($p < 0.02$) years old. The mean diameter of flare reaction by PPD was also the strongest in the patients between 30 and 49 years old. The flare reaction was considerably weaker in the subjects younger than 29 years and in the subjects over 50 years old. The flare in the patients aged between 30 and 49 years was significantly greater than in the patients under 29 ($p < 0.01$), between 50 and 59 ($p < 0.02$), between 60 and 69 ($p < 0.01$) and over 70 ($p < 0.01$) years old. These findings demonstrate that the

delayed skin reaction is considerably weaker in younger subjects and that the reaction begins to decrease in subjects over 50 years old (Fig. 1).

Delayed skin reaction to *C. albicans*. The mean diameter of induration by *C. albicans* was similar in all age groups under 69 years old. The diameter of induration was markedly decreased in the patients over 70 years old. A significant difference was found in the induration diameter between the 60-69 year old group and the group over age 70 years old. The mean diameter of flare reaction by *C. albicans* was the largest in the patients between 30 and 49 years old. The flare reaction tended to decrease with aging, although no significant difference was present between the 30-49 year old group and the 60-69 year old group. A significant difference was found in the flare diameter between the 60-69 year old group and the group over 70 years old ($p < 0.05$) (Fig. 2).

Relationship to serum IgE levels. The induration reaction to PPD was considerably stronger in the patients with a serum IgE level of 0-100 IU/ml and 101-300 IU/ml. The reaction decreased slightly with the elevation in serum IgE levels. The mean diameter of induration by PPD was significantly larger in the patients with a serum IgE level of 101-300 IU/ml than that in those levels between 501-1000 IU/ml ($p < 0.05$) and over 1001 IU/ml ($p < 0.05$). The flare reaction was the strongest in the

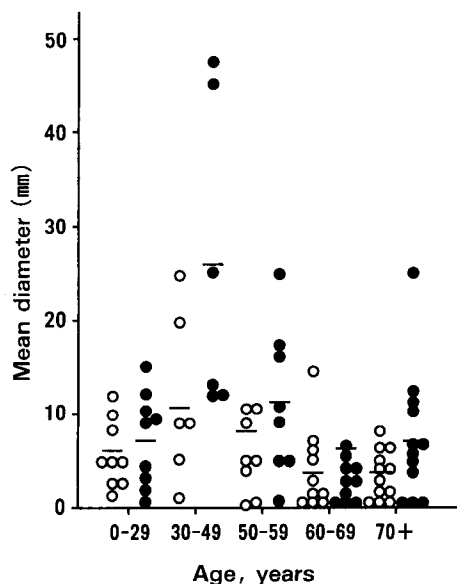


Fig. 1 Mean diameter of induration (○) and flare (●) induced by PPD in patients with bronchial asthma.

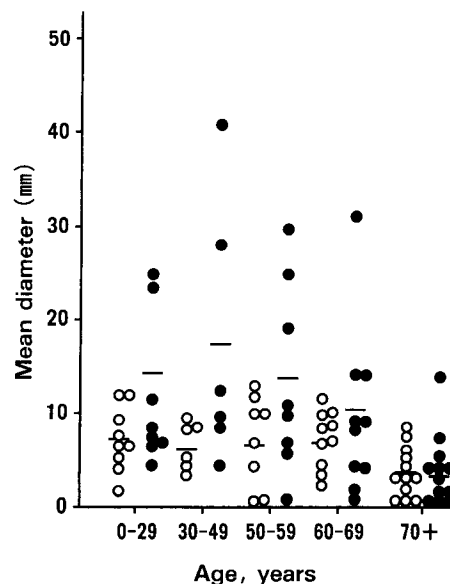


Fig. 2 Mean diameter of induration (○) and flare (●) induced by *C. albicans* in patients with bronchial asthma.

Table 1 Mean diameter of induration and flare reactions induced by PPD in relation to serum IgE level

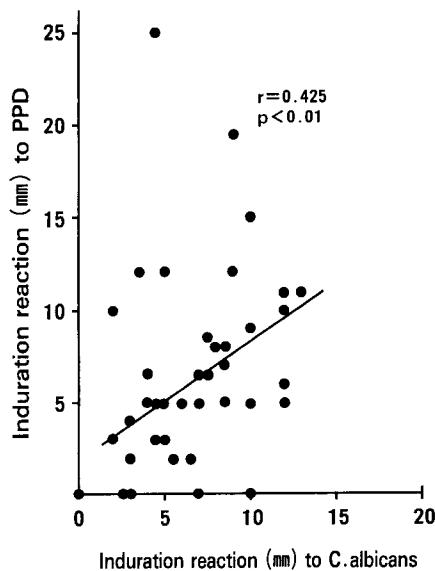
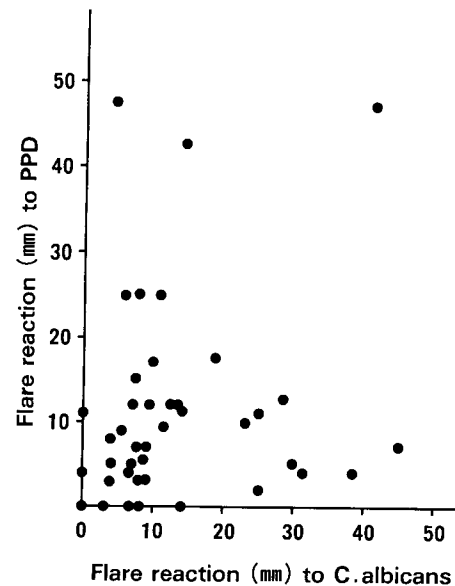
Serum IgE (IU/ml)	No of cases	Mean diameter (mm)*	
		Induration	Flare
0- 100	12	6.4 ± 7.2	12.3 ± 15.4
101- 300	13	8.4 ± 4.8 ^{ab}	13.2 ± 11.6
301- 500	6	3.8 ± 3.4	8.7 ± 8.0
501-1000	8	4.2 ± 3.3 ^a	5.6 ± 4.6
1001-	6	3.3 ± 3.4 ^b	5.1 ± 4.4

* Mean ± SD. Significant differences between corresponding values indicated *a* and *b* ($p < 0.05$).

Table 2 Mean diameter of induration and flare reactions induced by *C. albicans* in relation to serum IgE level

Serum IgE (IU/ml)	No of cases	Mean diameter (mm)*	
		Induration	Flare
0- 100	12	6.3 ± 3.6	9.3 ± 9.7
101- 300	13	7.3 ± 3.0 ^a	12.5 ± 10.2
301- 500	6	7.3 ± 4.4	19.3 ± 12.6 ^b
501-1000	8	4.4 ± 2.8	7.9 ± 7.9
1001-	6	3.8 ± 1.3 ^a	5.8 ± 5.0 ^b

* Mean ± SD. Significant differences between corresponding values indicated *a* and *b* ($p < 0.05$).

**Fig. 3** Correlation between induration reactions induced by PPD and *C. albicans*.**Fig. 4** Correlation between flare reactions induced by PPD and *C. albicans*.

patients with a serum IgE levels between 101-300 IU/ml and decreased slightly with the increase in the serum IgE level, but no significant difference was found among the six asthma groups (Table 1). Skin induration induced by *C. albicans* was decreased in the patients with a serum IgE levels over 1001 IU/ml. The skin reaction to *C. albicans* was significantly weaker in the patients with a serum IgE levels over 1001 IU/ml than in those with a serum IgE levels between 101-300 IU/ml ($p < 0.05$) for the induration reaction and between 301-500 IU/ml ($p < 0.05$) for the flare reaction (Table 2).

Correlation of reaction between C. albicans and PPD.

As shown in Fig. 3, the induration reaction to *C. albicans* was positively correlated with the reaction to PPD ($r = 0.425$, $p < 0.01$). The flare reaction against *C. albicans* showed no significant correlation with the reaction against PPD (Fig. 4).

Discussion

Depressed cell-mediated immunity is sometimes observed in atopic subjects (8, 15). In atopic subjects with depressed cell-mediated immunity, humoral immunity

associated with IgE, IgA, IgG and IgG₄ to *C. albicans* is increased (18, 19), because the cell-mediated immune system plays a major role in the defense against *C. albicans* (16). The cell-mediated immune response is also depressed with aging (19).

In the present study, the delayed cutaneous reactions to PPD and *C. albicans* were examined in relation to the patient's age and serum IgE levels, and the reactions to PPD and *C. albicans* were compared. The delayed skin reaction to PPD was considerably weaker in the younger patients under 29 years old. The reaction to PPD showed a decrease with aging starting in the 50 to 59 age group. It is interesting that the delayed skin reaction to *C. albicans* was stronger in the patients between 50 and 59 years old in whom the reaction to PPD was already depressed. The reason for the difference in age at the initiation of depressed cell-mediated immunity between PPD and *C. albicans* is unknown. The delayed reaction to both PPD and *C. albicans* was markedly depressed in the elderly patients over 70 years old.

The IgE-mediated allergic reaction seems to be associated with the depressed cell-mediated immunity in some atopic subjects. In the present study, the delayed skin reactions to PPD and *C. albicans* were depressed in patients with a serum IgE levels over 1001 IU/ml, and the patients with serum IgE levels below 100 IU/ml did not show a depressed cell-mediated immune response. These findings demonstrate that the cell-mediated immune response is affected by aging and by IgE-mediated reaction, and that the delayed skin reaction to *C. albicans* is still normal, not depressed even in patients between 50 and 69 years old, although the reaction to PPD is markedly depressed in these patients.

The delayed skin reactions to PPD and *C. albicans* are known to represent cell-mediated immunity. In this study, the delayed skin induration reactions to PPD and *C. albicans* were significantly correlated with each other, but the delayed skin flare reaction to PPD was not significantly correlated with the reaction to *C. albicans*.

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