◎総 説

Action mechanisms of complex spa therapy on bronchial asthma. 3. Relationship to airway inflammation

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Abstract : The degree and characteristic of airway inflammation were evaluated by the proportions of bronchoalveolar lavage (BAL) cells. Clinical asthma types such as I a. simple bronchoconstriction, I b. bronchoconstriction + hypersecretion, and II. bronchiolar obstruction correlate with airway inflammation. The increased proportion BAL neutrophils is characteristic of type II asthma, and increase in BAL eosinophil count is often observed in type I b asthma. Bronchial hyperresponsiveness also correlates with airway inflammation.

Action of spa therapy has been speculated to be related to airway inflammation, since the therapy has no action inhibiting IgE-mediated allergic reaction. In fact, spa therapy is more effective in patients with type I b and type II than in those with type I a showing slight degree of airway inflammation. Bronchial hyperresponsiveness is also improved by spa therapy. From a point of view, the direct action of spa therapy may be to clean airways and improve damaged mucous membrane of the airways, leading to suppression of airway inflammation.

Key word : Spa therapy, Airway inflammation, BAL eosinophilia, BAL neutrophilia, Bronchial asthma

Introduction

The symptoms of asthma are associated with such pathophysiological changes of the airways as bronchoconstriction, bronchial wall edema, and mucus hypersecretion. In addition to these pathophysiological changes, bronchiolar obstruction is clinically observed during asthma attacks [1, 2], and this is speculated to related inflammatory cell infiltra-

tion of small airways. In the onset mechanisms of asthma, humoral factors such as histamine and leukotrienes in the early stage of asthma attacks (IAR; immediate asthmatic reaction)[3-6], and cellular components such as lymphocytes, neutrophils, eosinophils, and basophils in the late stage (LAR; late asthmatic reaction) have been shown to play important roles[7-9]. Thus, airway inflammation accompanied with blood cell migration into allergic reaction sites is now considered to be a common pathological feature in asthma, particularly in the LAR[10-12]. Bronchial hyperresponsiveness is characteristic of patients with bronchial asthma. Airway inflammation is closely related to bronchial hyperresponsiveness.

Spa therapy is expected to improve late asthmatic reaction (LAR) accompanied with airway inflammation, but not to inhibit early stage of asthma attacks (humoral phase) (IAR) by IgE-mediated allergic reaction. Spa therapy also improves bronchial hyperresponsiveness. In this article, a correlation between spa effects and airway inflammation was discussed in relation to effects of the therapy associated with the proportions of BAL cells and bronchial reactivity to methacholine.

Airway inflammation and bronchial responsiveness

Bronchial hyperresponsiveness is closely related to airway inflammation[8, 13-16]. The correlation between the proportion of each type of BAL cells and bronchial hyperresponsiveness was examined in our previous study, by measuring bronchial reactivity to methacholine[17]. A significant correlation between the proportion of BAL eosinophils and bronchial reactivity was observed in patients with atopic asthma ($r = -0.67$, $p<0.05$) (Fig. 1). A stronger negative

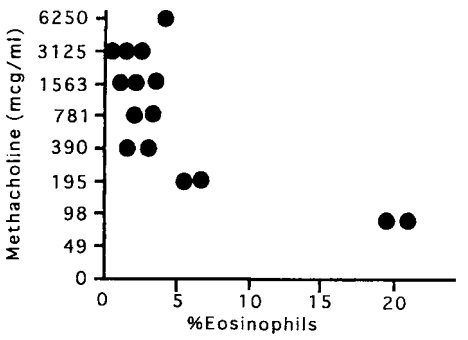

Fig. 1. Correlation between bronchial reactivity and proportion of eosinophils in BAL fluid in patients with atopic asthma ($r=-0.67$, $p<0.05$).

correlation was found in atopic subjects between the proportion of combined eosinophils (Eos) and neutrophils (Neut) and bronchial reactivity (BR) ($r=-0.71$, $P<0.05$) compared with that between the proportion of BAL eosinophils and BR (Fig. 2). In nonatopic asthmatics, a correlation between the proportion of BAL eosinophils and BR was also found ($r=-0.51$, $p<0.05$) (Fig. 3). There was, however, no correlation between the proportion of Eos + Neut in BAL fluid and BR. These results suggest that neutrophils as well as eosinophils participate in increase of bronchial responsiveness. An increased number of neutrophils in BAL fluid has been reported in patients with asthma[18], Furthermore, some reports suggest participation of neutrophils in bronchial hyperresponsiveness[19, 20].

Clinical asthma type

Bronchial asthma is classified into three types; I a. simple bronchoconstriction type, I b. bronchoconstriction+hypersecretion type

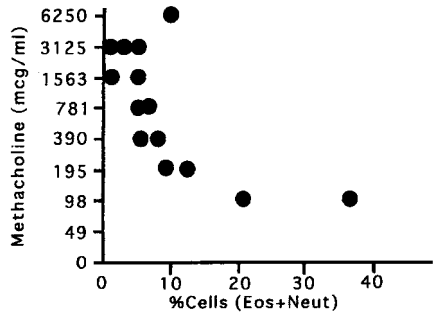

Fig. 2. Correlation between bronchial reactivity and proportion of eosinophils + neutrophils in BAL fluid in patients with atopic asthma ($r=-0.71$, $p<0.05$).

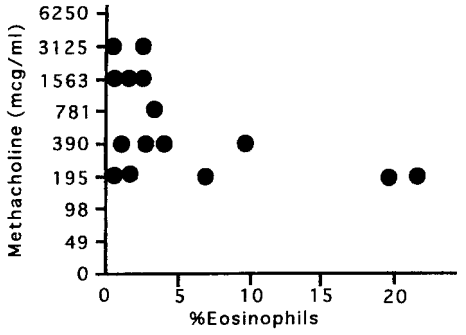

Fig. 3. Correlation between bronchial reactivity and proportion of eosinophils in BAL fluid in patients with nonatopic asthma ($r=-0.51$, $p<0.05$).

(expectoration more than 100 mℓ/day), and II. bronchiolar obstruction type, according to clinical symptoms.[21-24]. Type I a is, furthermore, divided into two subtypes according to expectoration per day; I a-1 (0−49mℓ/day) and I a-2 (50−99 mℓ/day).

There is a peculiar finding in the BAL cells regarding the proportion of neutrophils. The proportion of BAL neutrophils is significantly higher in type II than in the other types of asthma. Patients with type II asthma in general requires a long-term glucocorticoid therapy, leading to suppression of humoral and cellular immunity[25,26]. It is not clear whether an increase in the proportion of BAL neutrophils associated with suppressed immunity in type II asthma correlates with bronchial hyperresponsiveness. Thus, BAL neutrophilia is often observed in type II asthma, however, type II asthma without BAL neutrophilia has been found in our recent studies[27]. The proportion of eosinophils in BAL fluid, being closely related to hypersecretion in the airways[28], is higher in patients with type I a−2, type Ib and type II than in those with the other types of asthma (Fig. 4).

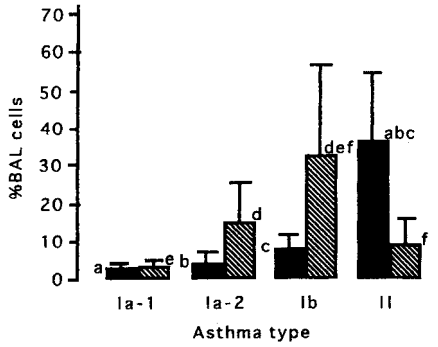

Fig. 4. Proportion of neutrophils (■) and eosinophils (▨) in the BAL fluid of patients with each clinical type of asthma. a, b, c, d, and f $p<0.001$, e, $p<0.02$

Spa efficacy and asthma type

Spa efficacy is different among three clinical asthma types, in our study on spa efficacy for each asthma type of 136 patients with asthma, the efficacy rate was 76.4% I b patients with simple bronchoconstriction (type I a), 82.6% in those with bronchoconstriction + hypersecretion (type I b), and 88.9% in those with bronchiolar obstruction

(type II)[29], showing that the efficacy rate was the highest in type II and the lowest in type I a. Type II asthma is always accompanied with obstruction of small airways, for which any antiasthma drugs except glucocorticoids are not effective. Spa efficacy for the pathophysiological changes of small airways is one of the most important role of the therapy[30].

Spa therapy suppresses hypersecretion of the airways in patients with asthma. In our previous studies on asthma patients with expectoration over 100 mℓ/day, the volume of expectoration before spa therapy (163mℓ/day) was significantly reduced to 56mℓ/day after 2-week spa therapy ($p<0.01$)[31]. A significant reduction was also observed after 4-, 5-, 6-, and 7-week spa therapy. although the volume of expectoration tended to increase 3 weeks after the therapy (Fig. 5). In terms of patient age, in those over the age of 60 with expectoration over 100mℓ/day, the volume decreased more rapidly and to a greater extent in those under age 59 with this volume of expectoration. However, this difference between the two age groups was not significant (Fig. 6). These results suggest that spa therapy is more effective in asthma patients in whom airway inflammation is clearly observed than in those with slight airway inflammation and in those whose attacks are mainly induced by immediate allergic reaction.

Patients with type I b and type II asthma tend to require long-term glucocorticoid regimen. In fact, majority of these patients has steroid-dependent intractable asthma (SDIA) Requirement of spa therapy for bronchial asthma is larger in patients with these types of asthma.

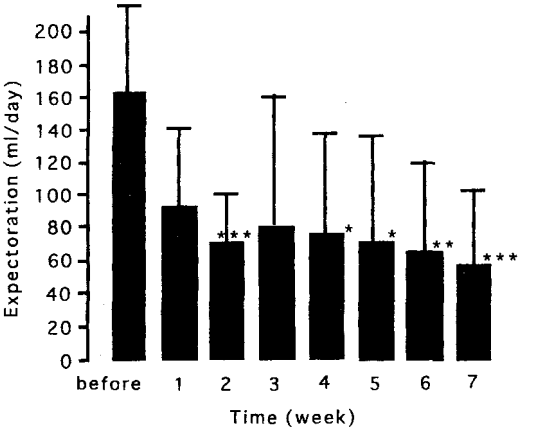

Fig. 5. Effects of spa therapy on airway mucus hypersecretion in asthmatic patients with expectoration over 100mℓ/day. *$p<0.05$, **$p<0.02$, ***$p<0.01$

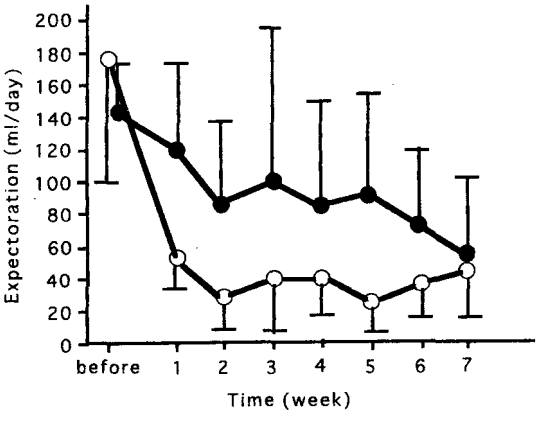

Fig. 6. Reduction of expectoration by spa therapy in asthmatic patients with expectoration over 100mℓ/day under the age of 59 (●—●) and in those over age 60 (○—○).

Spa therapy in patients with SDIA

Despite newly developed antiasthma drugs including antiallergic agents, sometimes physicians have a difficult task to treatment asthma attacks. There are some patients

whose symptoms can not be controlled by usual medications except glucocorticoids. Their attacks often begin to occur at middle age (so-called late onset asthma). Shortly after their attacks begin to occur, glucocorticoid therapy is required to control their attacks, leading to SDIA.

An important role of spa therapy is to have particular advantage in the treatment for patients with SDIA[33-36]. The therapy has direct and indirect effects on bronchial asthma. The dysfunction of airways, especially small airways, is improved by the direct action of spa therapy. In the indirect action of spa therapy[37,38], improvement of suppressed function of adrenocortical glands can be observed. The action is one of the most important roles of spa therapy for bronchial asthma, since the suppression of adrenocortical glands function is observed in the majority of these patients with SDIA. Thus, it has been expected that spa therapy acts effectively on bronchial asthma to normalize the function of airways and adrenocortical glands.

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気管支喘息に対する複合温泉療法の作用機序
3．気道炎症反応との関連

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気道炎症反応の程度や特徴が，気管支肺胞洗浄液（BAL）中の細胞成分によって評価された。Ⅰa．単純性気管支攣縮型，Ⅰb．気管支攣縮＋過分泌型，Ⅱ．細気管支閉塞型などの各臨床病型は気道炎症反応と関連している。BAL液中好中球増多は，Ⅱ型喘息の特徴的所見であり，また好酸球増多はIb型喘息でしばしば観察される。気道過敏性もまた気道炎症反応と関連している。

温泉療法の作用機序としては，温泉療法にIgEにmediate されるアレルギー反応（液性因子相）を抑制する作用がないことから，気道炎症反応（細胞性因子相）の抑制が推測されている。実際，温泉療法は，気道炎症反応が軽度なⅠa型喘息に比べ，Ⅰb型やⅡ型などの明らかに気道炎症反応をともなう病型に対してより有効である。気道過敏性もまた温泉療法により改善される。これらの結果から，温泉療法は，気道を清浄化し，気道粘膜を正常化することによって，気道炎症反応を抑制していくものと考えられる。

索引用語：温泉療法，気道炎症反応，BAL好酸球増多，BAL好中球増多，気管支喘息