Mini Review

Role of cysteinyl-leukotrienes in the pathogenesis of nasal polyposis in patients with asthma

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Cysteinyl leukotrienes (CysLTs: leukotrienes C_4, D_4, and E_4) have long been implicated in the pathogenesis of allergic diseases such as asthma. CysLTs are potent bronchoconstrictors that have the additional effects of edema, mucous secretion, and eosinophilic accumulation, and airway remodeling. LTE_4 has been identified as a major metabolite of LTC_4, and urinary LTE_4 ($U\text{-}LTE_4$) is considered as the most reliable analytic parameter for monitoring the endogenous synthesis of CysLTs. From our extensive study of $U\text{-}LTE_4$ in adult asthma, we identified four factors for hyperleukotrienuria. These factors were aspirin-intolerance, eosinophilic nasal polyposis (ENP), vasculitis, and severe asthma. In ENP there is prominent infiltration of eosinophils in the sinus and polyp tissues, which is linked to adult asthma and aspirin-sensitivity, and ENP is the most important factor for overproduction of CysLTs in asthmatics. We demonstrated that there is a significant decrease in the $U\text{-}LTE_4$ concentration after the sinus surgery of asthmatics with and without aspirin intolerance. Recent studies reported that ENP tissue contain and produce a large amount of CysLTs, and there is a close relationship between CysLT production and eosinophil accumulation in ENP. These observations suggest that ENP is not only a local allergic disease, but also a systemic inflammatory disease with CysLT overproduction.

Rec.2/19/2007, Acc.5/7/2007, pp565-569

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Key words eosinophilic sinusitis, asthma, cysteinyl-leukotriene, nasal polyposis, aspirin-intolerant asthma

Cysteinyl leukotrienes, asthma, and eosinophilic inflammation

Leukotrienes (LTs) are among lipid mediators formed from the enzymatic metabolism of arachidonic acid (AA), and are the first biologic substances confirmed to have importance in the clinical course of asthma and the physiologic changes of asthma. Both the cysteinyl leukotrienes (CysLTs), namely leukotriene C_4 (LTC_4), LTD_4, and LTE_4, and leukotriene B_4 (LTB_4) have long been implicated in the pathogenesis of allergic diseases such as asthma[1]. CysLTs are potent bronchoconstrictors that have the

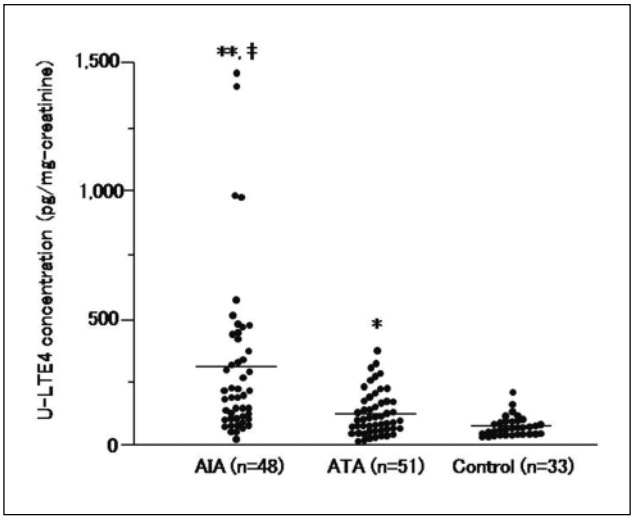

Fig.1 Basal levels of urinary LTE4 in patients with aspirin-intolerant asthma (AIA) and patients with aspirin-tolerant asthma (ATA).

Horizontal bars indicate geometric means.

* $p < 0.001$ compared with the control group; ** $p < 0.0001$ compared with the control group; ‡ $p < 0.0001$ compared with the ATA group. (Adapted from Kawagishi et al.[15])

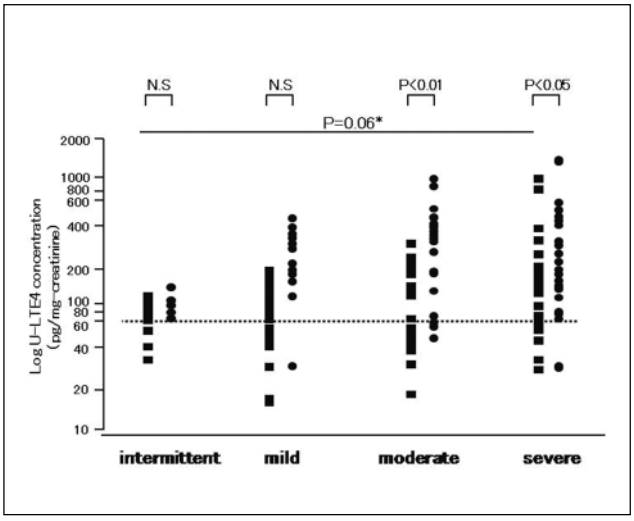

Fig.2 U-LTE4 concentration in patients with aspirin-intolerant asthma (AIA) and patients with aspirin-tolerant asthma (ATA) classified according to clinical severity of asthma.

U-LTE4 concentration is expressed by using the log scale. Patients with ATA and patients with AIA are denoted by closed square and an open circle, respectively. The dotted line indicates the mean level of U-LTE4 in healthy control subjects.

* U-LTE4 concentrations in patients with ATA with different clinical asthma severity levels were compared by using the Kruskal-Wallis test. (Adapted from Higashi et al.[14])

additional effects of edema, mucous secretion, and eosinophilic inflammation[2-4]. Recently, several reports demonstrated that CysLTs also have two other important effects, namely trafficking of eosinophils[5,6] and induction of airway remodeling[7,8].

The $CysLT_1$ receptor is detected mainly on eosinophils, mast cells, and smooth muscle cells. Inhalation of LTE_4 has been shown to lead the infiltration of eosinophils into the lungs of asthmatic patients[9]. *In vitro* studies of the chemoattractant properties of CysLTs have shown only marginal effects of LTD4[10]. If present, chemoattractant activity may occur through the secondary activation of the eosinophil chemoattractant and activator. In addition, a recent study suggests that CysLTs are important for prolonging eosinophil survival, which may also explain the increased-numbers of eosinophils after CysLTs inhalation. LTD_4 appears to have potency similar to that of granulocyte-macrophage colony-stimulating factor (GM-CSF) in this regard[11]. LT receptor antagonists (LTRAs) and synthesis inhibitors were able to abolish the effect of eosinophil apoptosis, suggesting that this occurs in an autocrine manner through the $CysLT_1$ receptor[11].

Asthma with hyperleukotrieneuria

LTs are downstream products of the metabolism of cell or nuclear membrane phospholipids. In certain inflammatory cells e.g., eosinophils, mast cells, other inflammatory cells, degradation to AA by phospholipase A2 occurs at the nuclear membrane, which indicate the biologic functions of the LTs once they are formed[1-4]. 5-lipoxygenase (5-LO) activation at the cytoplasmic or nuclear membrane then leads to the production of an unstable intermediate known as LTA_4, which can be further metabolized, depending on cell type, to LTB_4 or the cysLTs (LTC_4, LTD_4, and LTE_4). LTC_4 synthase metabolizes LTA_4 to LTC_4 via a glutathione transferase. LTC_4 is then rapidly metabolized to LTD_4 and LTE_4 through the enzymes gamma-glutamyl transpeptidase. LTC_4 and LTD_4 both have very short half-lives, whereas LTE_4 appears to be the most stable of the three, with the longest half-life[12].

LTE_4 has been identified as a major metabolite of LTC_4, recently, urinary LTE_4 ($U\text{-}LTE_4$) has been considered as the most reliable analytic parameter for monitoring the endogenous synthesis of CysLT[13]. Previous studies showed that $U\text{-}LTE_4$ concentration is useful for demonstrating CysLT production *in vivo* during allergen challenge and an acute attack of asthma[13]. More-

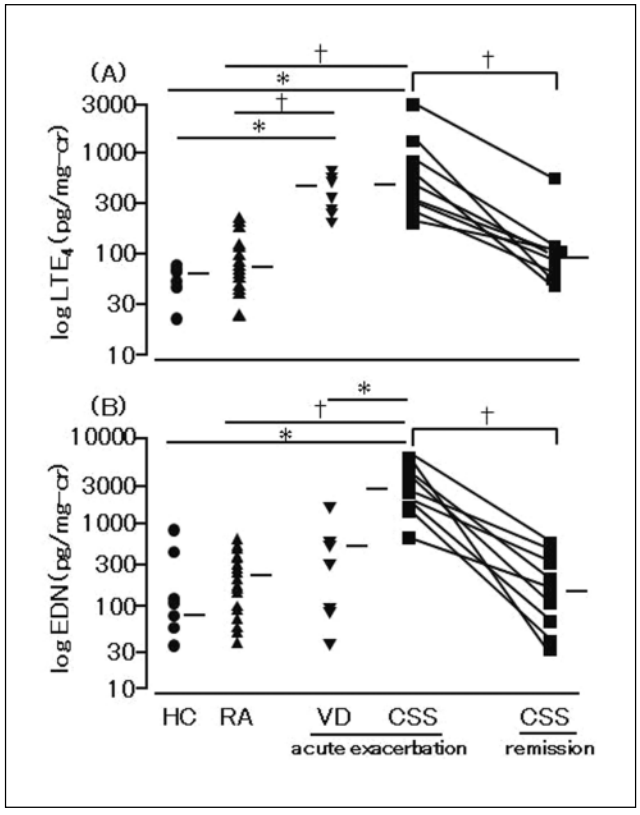

Fig.3 U-LTE4 (A) and eosinophil derived neurotoxin (EDN,B) concentrations in patients with Churg-Strauss syndrome (CSS), noneosinophilic vasculitis (VD), rheumatoid arthritis (RA), and healthy control (HC).

U-LTE4 concetration is expressed by using the log scale. The horizontal bars indicate medians.

* $p < 0.05$; † $p < 0.01$. (Adapted from Higashi et al.[17])

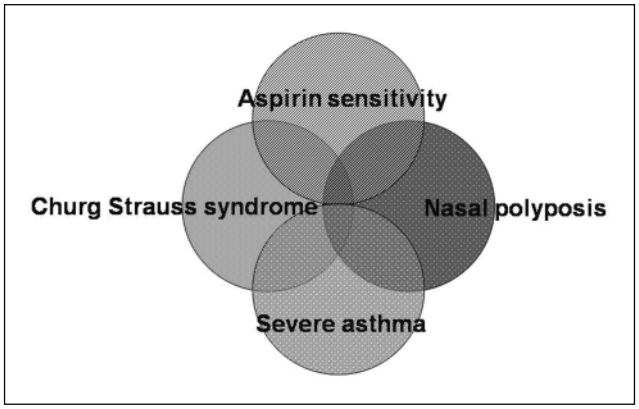

Fig.4 The four clinicopathological factors assoiated with hyperleukotrienuria in adult asthmatics.

over, even in a clinically stable condition, U-LTE4 concentration in patients with aspirin-intolerant asthma (AIA) is significantly higher than that in patients with aspirin-tolerant asthma (ATA)[14,15]. Recently, we have evaluated the clinicopathological factors that were associated with the increase in U-LTE4 concentration in asthmatics and we confirmed that U-LTE4 concentration in AIA patients was significantly higher than those in ATA patients (Fig.1). According to asthma severity, ATA patients with severe asthma and AIA patients with poor pulmonary function showed a significant increase in U-LTE4 concentration, but the extent of increase in U-LTE4 concentration was not large (Fig.2)[14]. Moreover, we have demonstrated for the first time that nasal polyposis is one of the most important factors indicating hyperleukotrienuria[14]. Recently, we have determined another clinicopathological factor for hyperleukotrienuria in patients with adult asthma. Churg-Strauss syndrome (CSS) is characterized by the presence of asthma, eosinophilia, and small-vessel vasculitis with granuloma[16]. The natural history of CSS is, first, the appearance of eosinophilic rhinosinusitis, followed several years later by the development of difficult asthma with marked peripheral blood eosinophilia, and finally the development of systemic vasculitis[16]. We have demonstrated that U-LTE4 concentration is elevated in the acute phase of CSS[17]. However, U-LTE4 concentration significantly increases in not only eosinophilic vasculitis, including CSS, but also noneosi-nophilic vasculitis (Fig.3)[17].

From these observations, we postulate that the four clinicopathological factors associated with hyperleukotrienuria in adult asthmatics were firstly aspirin-intolerance, secondly nasal polyposis, thirdly CSS, and finally (this is not so important factor) severe asthma (Fig.4).

Role of cysteinyl-leukotrienes in the pathogenesis of nasal polyposis

Nasal polyps are edematous semitranslucent masses in the nasal and paranasal cavities, mostly originating from the mucosal linings of the sinuses and prolapsing into the nasal cavities. Eosinophilic nasal polyposis (ENP), in which there are prominent infiltration of eosinophils and submucosal edema, is linked to comorbidities such as nonatopic asthma, adult-onset asthma, aspirin intolerance, or may represent a part of a systemic disease such as CSS[16,18]. Despite sinus surgery or intensive steroid therapy, the recurrence rate of ENP in patients with asthma is very high, and the pathogenesis of ENP has not been clarified[18].

For the first time, we found that the U-LTE4 concentration is significantly high even in ENP patients without aspirin-sensitiv-

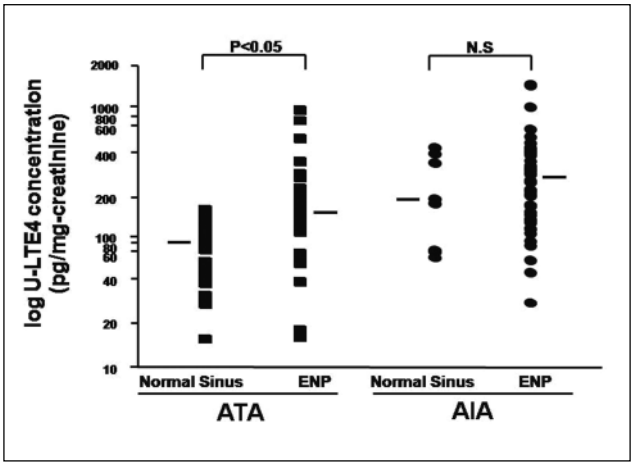

Fig.5 U-LTE$_4$ concentration in patients with eosinophilic nasal polyposis (ENP) and those with normal sinuses.

U-LTE$_4$ concetration is expressed by using the log scale. The horizontal bars indicate medians. (Adapted from Higashi et al.[14])

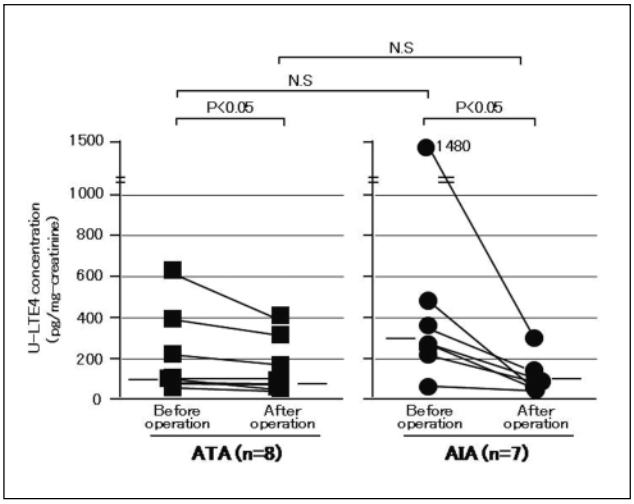

Fig.6 A significant decrease in U-LTE$_4$ comcentration between before and after the endoscopic sinus surgery without changing medication.

The horizontal bars indicate medians. (Adapted from Higashi et al.[14])

ity (Fig.5). Next we confirmed the changes in U-LTE$_4$ concentration after endoscopic sinus surgery without changing medication. We demonstrated that U-LTE$_4$ concentrations significantly decreased after the sinus surgery in both AIA and ATA (Fig.6)[14]. Steinke et al. reported that CysLT concentrations in ENP tissues are significantly higher than those in noneosinophilic nasal polyp tissues[19]. They also demonstrated that the presence of CysLTs in ENP is associated with an increased expression level of LTC$_4$ synthase mRNA[19]. Perez-Novo et al. confirmed that the concentrations of CysLTs, eosinophil cationic protein (ECP), and the expression level of LTC$_4$ synthase mRNA in ENP tissues were significantly higher than those in the tissue with sinusitis without polyps[20]. From our findings and recent reports[19,20], we conclude ENP tissues contain and produce large amounts of CysLTs, and that there is a close correlation between CysLT production and eosinophil accumulation in ENP. CysLTs have several inflammatory effects on eosinophils, which are not only activation, but also the effect of trafficking and inhibition of apoptosis[5,6]. Eosinophils are among the CysLTs producing-cells, and also have the CysLT$_1$ receptor. The phenomena of eosinophil accumulation and CysLTs overproduction in ENP seem to comprise a malignant cycle in allergic inflammation.

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