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Differences in urinary leukotriene E4 levels and distribution of eosinophils between chronic rhinosinusitis patients with aspirin-intolerant and -tolerant asthma

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ABSTRACT

Objective: Urinary leukotriene E4 (U-LTE4) concentrations are significantly elevated in patients with aspirin-intolerant asthma (AIA). However, the relationship between the clinicopathogenetic features of eosinophilic rhinosinusitis and U-LTE4 concentration remains unknown. Here we examined the relationship between U-LTE4 level and eosinophil in chronic rhinosinusitis.

Methods: We measured the U-LTE4 concentrations and eosinophil counts in ethmoidal and maxillary sinuses and peripheral blood in 30 asthmatic patients (including 15 AIA patients).

Results: Eosinophil counts in ethmoidal sinuses and peripheral blood were markedly higher in asthmatic patients than in controls. Although there were no significant differences between eosinophil counts in maxillary and ethmoidal sinuses for ATA group, eosinophil counts were higher in ethmoidal sinus compared to that in maxillary sinus in the AIA group ($P < .05$). Eosinophil counts were higher in the maxillary than in ethmoidal sinuses for control patients ($P < .05$). Despite low correlation between eosinophil counts in peripheral blood and eosinophil counts in maxillary sinus (rs = 0.4323, $P < .001$), moderate correlation was observed between eosinophil counts in peripheral blood and eosinophil counts in ethmoidal sinus (rs = 0.5249, $P < .0001$). Basal U-LTE4 concentrations were higher in AIA patients than in those with aspirin-tolerant asthma. Despite low correlation between eosinophil counts and U-LTE4 concentration in maxillary sinus (rs = 0.3849, $P < .01$), moderate correlation was observed between eosinophil counts and U-LTE4 concentrations in ethmoidal sinus (rs = 0.4736, $P < .001$).

Conclusion: We describe the differences in U-LTE4 and other parameters in AIA compared to ATA, and correlation among parameters. We demonstrate that eosinophil-dominant inflammation starts in ethmoidal sinus clinicopathogenetically in CRS with asthma. U-LTE4 concentration was not exclusively associated with eosinophil counts in ethmoidal sinus. Eosinophils in ethmoidal sinus may be a major production site for CysLTs, particularly in AIA. CRS with AIA is assumed to be characterized by leukotriene-eosinophil cross-interaction in ethmoidal sinus.

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1. Introduction

Some types of chronic rhinosinusitis (CRS) are less responsive to standard therapy and have a higher tendency to recur. Strong eosinophil infiltration may be observed in the nasal polyps and lamina propria of patients with a type of CRS, known as eosinophilic CRS (ECRS). This term was coined by Haruna et al. in 2001 [1]. ECRS is characterized by inflammation in the ethmoid sinus, anosmia, high frequency of nasal polyp recurrence, and increased eosinophil count in the nasal membrane and blood. However, the study by Haruna et al. described the inflammatory characteristics by computed tomographic evaluation without the evaluation of histological eosinophil distribution.

Steinke et al. reported that eosinophilic nasal polyp tissue contains and produces a large amount of cysteinyl leukotrienes (CysLTs) and that there is a close relationship between CysLT production and eosinophil accumulation in eosinophilic nasal polyps [2].

Nasal polyp tissue may produce CysLTs in case of aspirin-intolerant asthma (AIA) and aspirin-tolerant asthma (ATA), and such CysLTs may have systemic effects. However, Steinke et al. did not describe any quantitative differences in eosinophilic infiltration among the sinuses. We can determine the primary site of inflammation and leukotriene production by anatomically and quantitatively studying eosinophilic infiltration.

CysLTs are important mediators that cause potent bronchoconstriction, mucosal edema, and increased mucus secretion within the airways of asthmatic patients. CysLTs are produced by eosinophils, mast cells, basophils, and monocytes [3,4]. They help impede the cycle in which CysLTs and chemotactic factors are produced by eosinophils via CysLT1 receptors on eosinophils. In contrast, leukotriene E4 (LTE4) has been identified as a major metabolite of LTC4 [5,6], and U-LTE4 is now considered to be the most reliable index for monitoring endogenous CysLT synthesis [7,8].

Therefore, we hypothesized that CysLTs make CRS intractable, and we studied the eosinophilic infiltration of the ethmoid and maxillary sinus mucosa, following extraction during ESS and preoperative CysLTs.

The aims of this study were to determine the (1) characteristics of CRS with bronchial asthma based on anatomical eosinophil distribution and (2) characteristics of CRS with AIA.

2. Materials and methods

2.1. Subjects

This hospital-based, case–control study was conducted from July 2009 to December 2014. The study comprised 58 patients (mean age, 51.0 years; range, 23–75 years; 21 males and 37 females). CRS diagnosis was based on the European Position Paper on Rhinosinusitis and Nasal Polyps [9]. We divided the patients with CRS into three groups: (1) CRS with AIA, (2) CRS with ATA, and (3) CRS without bronchial asthma (control). There were 15 patients with AIA (mean age, 51.1 years; range, 28–72 years; 4 males and 11 females), 15 with ATA (mean age, 50.6 years; range, 33–73 years; 6 males and 9 females), and 28 non-asthmatic controls who showed bilateral sinusitis on computed tomography (mean age, 51.1 years; range, 23–75 years; 11 males and 17 females; Table 1). Asthma diagnosis was based on the American Thoracic Society criteria [10]. Before and after ESS for CRS, all patients were clinically stable, with no recent changes in asthma symptoms or medications. The patients were receiving only inhaled steroids, leukotriene receptor antagonists, and short-acting β2-agonists, but no systemic corticosteroids. The diagnosis of AIA was made on the basis of a positive result obtained in an aspirin challenge test or an obvious history of asthma attacks precipitated by NSAID administration. The patients with ATA and healthy controls had a negative aspirin challenge test result or took aspirin or other NSAIDs without any adverse symptoms [11]. The patients who had serum IgE levels of greater than 350 U/mL [11] were classified as atopic. No patient had cystic fibrosis, immotile cilia syndrome, Churg–Strauss syndrome, or autoimmune diseases, and none had upper respiratory tract infections during the six weeks immediately preceding the study. Permission to conduct the study was obtained from the ethics Committee of the National Sagamihara Hospital, and all patients provided informed consent.

2.2. Study design

We collected blood, urine, and sinus tissue samples from the patients. We determined peripheral blood eosinophil counts using a standard automated cell counter. Because β2-agonists, inhaled corticosteroids, sodium cromoglycate, or oral leukotriene receptor antagonists do not affect U-LTE4 levels [12], these medications were not withheld at the time of urine sample collection. To confirm the relationship between CRS and increased U-LTE4 excretion level, we compared LTE4 urine concentrations within one month before elective endoscopic surgery for CRS.

2.3. Clinical evaluation

All enrolled patients subsequently provided a detailed medical history, and they were examined to evaluate the presence of asthma and questioned regarding the use of medications, particularly topical nasal and systemic corticosteroids.

2.4. Pathological examination

The mucosal tissues of patients with CRS were removed from the nasal polyps or ethmoid and maxillary sinus at the time of functional ESS. We obtained the maxillary sinus membrane and polyps around membranous portions and the ethmoid sinus mucosa following uncinate process resection. The tissue was immediately fixed in 10% formalin, embedded in paraffin, and cut into thin sections. The sections were stained with hematoxylin–eosin. Nasal polyps were categorized as ethmoid or maxillary tissue with a stem base. We used the proposed diagnosis of Haruna et al. as a reference for eosinophilic sinusitis [1]. The number of eosinophils in the mucosa was counted under high-power field (400×) for fields in which eosinophils were the densest cellular infiltrate beneath the