

# Correlation between the Prostaglandin D<sub>2</sub>/E<sub>2</sub> Ratio in Nasal Polyps and the Recalcitrant Pathophysiology of Chronic Rhinosinusitis Associated with Bronchial Asthma

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## ABSTRACT

**Background:** The prevalence of patients with chronic rhinosinusitis (CRS) refractory to traditional therapy appears to be on the increase. In these cases, CRS tends to be associated with bronchial asthma (BA), especially, aspirin-intolerant asthma (AIA). On the other hand, arachidonic acid metabolites have been extensively investigated in the pathogenesis of BA. We sought to assess the role of prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) in the recalcitrant pathophysiology of CRS.

**Methods:** Samples were prepared from the nasal polyps and mucosa of 40 patients undergoing endoscopic sinus surgery (ESS) at our hospital. The nasal polyp specimens obtained from the patients with CRS were divided into three groups, as follows: the CRS-AIA group, consisting of specimens obtained from patients with CRS complicated by AIA, the CRS-ATA group, consisting of specimens obtained from patients with CRS associated with aspirin-tolerant asthma (ATA), and the CRS-NA group, consisting of specimens obtained from CRS patients without BA. PGD<sub>2</sub> and PGE<sub>2</sub> were extracted from the specimens and quantified.

**Results:** The concentrations of PGD<sub>2</sub> were significantly higher in the nasal polyps of the CRS-ATA group. The concentrations of PGE<sub>2</sub> were lowest in the nasal polyps of the CRS-AIA group. The PGD<sub>2</sub>/PGE<sub>2</sub> ratio was highest in the CRS-AIA group.

**Conclusions:** It has previously been reported that CRS complicated by AIA is most likely to be characterized by repeated remissions and relapses, and is thus the most intractable. We may therefore say that the PGD<sub>2</sub>/PGE<sub>2</sub> ratio reflects the intractable nature of CRS.

## KEY WORDS

aspirin-intolerant asthma, bronchial asthma, chronic rhinosinusitis, prostaglandin D<sub>2</sub>, prostaglandin E<sub>2</sub>

## INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory condition of the paranasal mucous membrane, characterized by the accumulation of eosinophils, fibroblasts, mast cells and goblet cells.<sup>1-3</sup> Nasal polyposis is frequently associated with other conditions, such as bronchial asthma (BA),<sup>4-6</sup> including aspirin-intolerant asthma (AIA).<sup>7</sup> Recently, although there has been an

increase in the cure rates of patients with CRS, with the institution of low-dose long-term treatment with macrolide antibiotics and adoption of endoscopic sinus surgery (ESS),<sup>8,9</sup> there still remains a substantial number of patients with a poor prognosis.<sup>10</sup> Such patients with a poor prognosis have been found to include a high proportion of patients with lower respiratory tract disorders, such as BA.

BA is a chronic inflammatory disorder character-

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Received 19 February 2008. Accepted for publication 30 June 2008.

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**Table 1** Patient clinical data

	Control	CRS-NA	CRS-ATA	CRS-AIA
N	7	14	12	7
Sex (F/M)	1/6	2/12	3/9	2/5
Age average	32.43 ± 10.26	44.14 ± 16.08	43.75 ± 14.42	48.43 ± 18.75
Age range	19–46	20–71	18–65	26–71
Total IgE	101.71 ± 81.41	100.25 ± 142.65	257.91 ± 258.73	206.86 ± 374.13
Peripheral blood eosinophils (%)	3.78 ± 2.56	2.57 ± 1.26	8.33 ± 4.44	13.39 ± 9.88

ized by mast cell and eosinophilic infiltration of the airways. BA can be categorized into two distinct types according to the presence or absence of aspirin sensitivity: aspirin-intolerant asthma (AIA) and aspirin-tolerant asthma (ATA). In particular, AIA is a distinct clinical syndrome affecting a significant proportion of adult patients with BA, in whom aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) precipitate bronchoconstriction.<sup>11,12</sup> Patients with AIA often have a particularly severe form of BA, associated with rhinorrhea and recurrent polyp formation.<sup>11,12</sup>

Arachidonic acid metabolites have been extensively investigated in the pathogenesis of BA. Cysteinyl leukotrienes (CysLTs), strong proinflammatory factors generated from arachidonic acid through the 5-lipoxygenase pathway, have been recognized as the key mediators of an asthmatic attack.<sup>13</sup> CysLTs are components of the slow-reacting substance of anaphylaxis (SRS-A) and have been shown to have profound effects on the airways,<sup>14,15</sup> e.g., able to induce airway smooth muscle contraction and vasodilatation, enhance vascular permeability, and alter the remodeling process in asthma.<sup>16,17</sup> Prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) is a potent bronchoconstrictor and its effect is mediated by the TP receptor.<sup>18</sup> Therefore, PGD<sub>2</sub> may be an important mediator of airway smooth muscle contraction in an immediate asthmatic reaction.<sup>19</sup> Furthermore, it has recently been reported from experiments using knockout mice that PGD<sub>2</sub> exacerbates asthma.<sup>20,21</sup> In contrast, prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) protects airways against inflammation and promotes normal airway function.<sup>22,23</sup> On the other hand, PGE<sub>2</sub> enhances immunoglobulin (Ig) E production. PGE<sub>2</sub> promotes IL-4 production from Th2 cells, suppresses IFN- $\gamma$  production from Th1 cells, and promotes IgE production from B cells.<sup>24</sup>

As described above, a large number of reports have been published concerning the involvement of arachidonic acid metabolites in the pathophysiology of BA. It seems probable that arachidonic acid metabolites are among the factors responsible for the intractable course of CRS as well. Taking into account this possibility, additionally there have been recent reports that PGD<sub>2</sub> and PGE<sub>2</sub> are closely involved in airway inflammation<sup>25-27</sup> and that the balance between PGD<sub>2</sub> and PGE<sub>2</sub> production determines the se-

verity of inflammation in various inflammatory conditions.<sup>28-30</sup> Consequently, we undertook the present study in which patients with CRS associated with BA were divided according to whether they had ATA or AIA, and the amounts of PGD<sub>2</sub> and PGE<sub>2</sub> in the nasal polyps were compared between patients with intractable CRS complicated by ATA and those with CRS complicated by AIA.

## METHODS

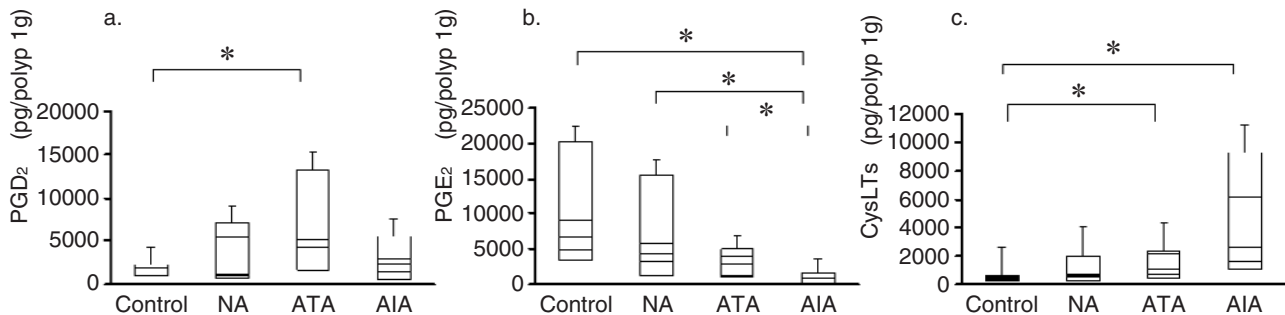
### SUBJECTS

Nasal polyp tissue specimens were obtained at the time of surgery from subjects ( $n = 33$ ) referred to Jikei University Hospital for ESS. To examine the role of the arachidonic acid metabolites in the pathogenesis of CRS, the specimens were obtained from CRS patients classified into 3 subgroups, as follows: CRS without BA (CRS-NA group;  $n = 14$ ), CRS associated with ATA (CRS-ATA group;  $n = 12$ ), and CRS associated with AIA (CRS-AIA group;  $n = 7$ ). In addition, specimens from 7 controls were also examined (5 middle turbinate mucosa specimens obtained from patients with non-allergic rhinitis and 2 middle meatus mucosa specimen obtained from a blowout fracture patient). Informed consent was obtained from all of the patients prior to their enrollment in the study, and the study was approved by the ethics committee at the Jikei University Hospital. The clinical data of the patients are summarized in Table 1. Before the ESS, measurements of the serum IgE levels and peripheral blood eosinophil counts, as well as sinus computed tomographic (CT) studies, were performed for each patient.

### CLINICAL ASSESSMENT

The diagnosis of CRS was based on the typical symptoms (nasal congestion, dysosmia, etc.) as assessed from the documented medical history, the presence of endoscopically visible nasal polyps arising from the middle nasal meatus, and involvement of the ethmoidal and maxillary sinuses as visualized in limited CT scans of the paranasal sinuses.

The diagnosis of asthma was made at the Department of Pulmonology, Jikei University Hospital, based on the documented clinical history of the typical symptoms. The diagnosis of AIA was based on a history of asthma exacerbation, nasal congestion, and



**Fig. 1** PGD<sub>2</sub> (a), PGE<sub>2</sub> (b) and CysLTs (c) concentrations in the nasal polyps. Between-group comparisons were performed by Mann-Whitney's *U*-test with Bonferroni correction (\**p* < 0.05).

or rhinorrhea after the ingestion of aspirin or other nonsteroidal anti-inflammatory drugs.

### QUANTIFICATION OF ARACHIDONIC ACID METABOLITES

The nasal polyp tissue specimens were homogenized in ethanol to extract the lipid fraction, the arachidonic acid metabolites were stabilized, and the cellular protein was removed. After centrifugation of the precipitated proteins, the supernatants were dried, resuspended in 80% ethanol and loaded on to a C18 Sep-Pak column (Waters, Milford, MA). This column was rinsed with ultra pure water followed by ethyl acetate, and the arachidonic acid metabolites were then eluted with ethanol/water (90 : 10). PGD<sub>2</sub>, PGE<sub>2</sub> and CysLTs were quantified using a high-sensitivity competitive enzyme immunoassay kit (EIA kit; Cayman Chemical, Ann Arbor, MI, USA), in accordance with the manufacturer's directions. The EIA is a competitive sandwich enzyme-linked immunosorbent assay technique, and the data were determined in comparison with standards for arachidonic acid metabolites. Data were expressed as picograms of PGD<sub>2</sub>, PGE<sub>2</sub> and CysLTs per gram of nasal polyp tissue in the original homogenate.

### IMMUNOHISTOCHEMICAL ANALYSIS

Monoclonal antibodies against human eosinophil cationic protein (EG2; Pharmacia, Uppsala, Sweden) and mast cell tryptase (Chemicon International, Temecula, CA, USA), CD68 (Dako Cytomation, Glostrup, Denmark) were used for the immunohistochemical analysis. Immunostaining with the avidin-biotin complex was performed as described previously.<sup>31</sup> In brief, deparaffinized sections were initially incubated with 3% H<sub>2</sub>O<sub>2</sub> in methanol for 15 minutes to quench the endogenous peroxidase activity, washed twice with TBS (Dako Cytomation) and incubated overnight at 4°C with the primary antibody specific for EG2, mast cell tryptase or CD68; they were then washed and incubated for 30 minutes with Envision/AP<sup>®</sup> (Dako, Cambridgeshire, UK) or Envision+<sup>®</sup> (Dako). After being washed again with TBS, color de-

velopment was conducted using Fast Red (Sigma, Poole, UK) or diaminobenzidine (DAB; Dako) as the chromogen for signal visualization. Using this method, the cells expressing tryptase or CD68 were visualized in brown color (using DAB) while those expressing EG2 were red in color (using Fast Red). Negative controls were prepared by replacing the primary antibodies with isotype immunoglobulin.

Cells in the coded biopsy sections were counted by an investigator blinded to the protocol. The cells showing positive immunostaining in the nasal submucosal region where the highest cellular infiltration was seen were counted under a microscope. Then, the average number of positive cells in three high-power fields (200× or 400×) was determined.

### STATISTICAL ANALYSIS

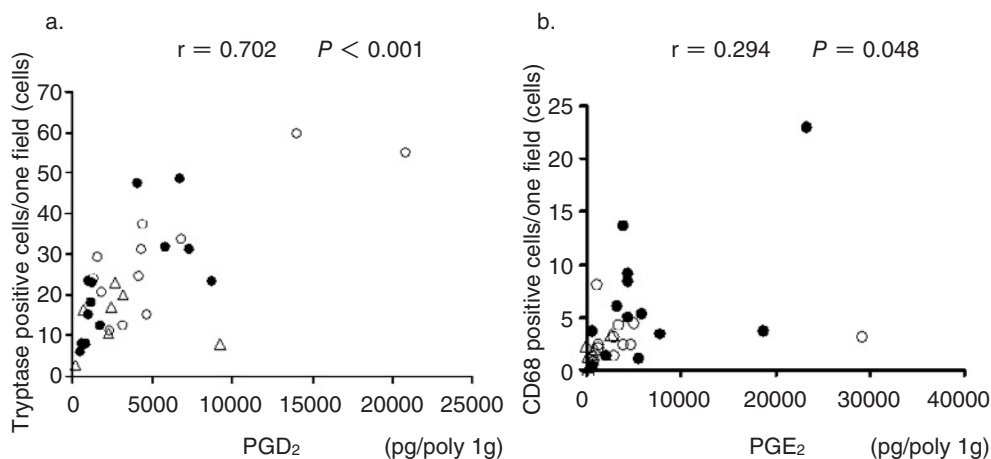
All the statistical analyses were nonparametric. Between-group comparisons were performed by the nonparametric Mann-Whitney's *U*-test with Bonferroni correction. Correlation analysis was performed using Spearman's rank correlation coefficient. Differences (two-sided) were considered significant when the *P* value was less than 0.05.

### RESULTS

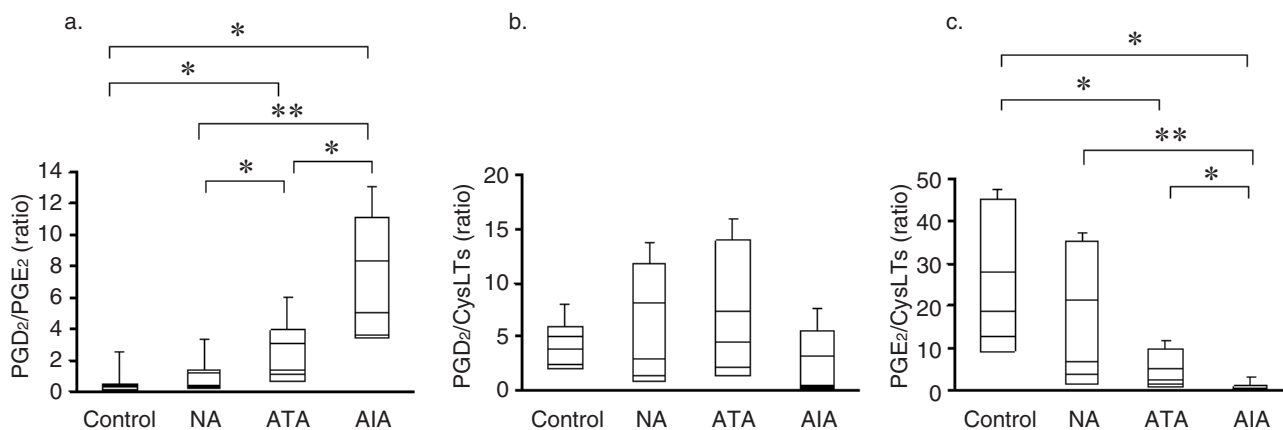
#### PGD<sub>2</sub>, PGE<sub>2</sub> AND CysLTs CONCENTRATIONS IN THE NASAL POLYPS

The concentrations of PGD<sub>2</sub>, PGE<sub>2</sub> and CysLTs determined in the nasal polyps are summarized in Figure 1. The concentrations of PGD<sub>2</sub> were significantly higher in the nasal polyps of the CRS-ATA group as compared with those in the control specimens (*P* = 0.035, Fig. 1a). The concentrations of PGD<sub>2</sub> tended to be higher in the nasal polyps of the CRS-ATA group than in those of the CRS-AIA group, but this difference was not statistically significant.

The concentrations of PGE<sub>2</sub> were highest in the control specimens and lowest in the nasal polyps of the CRS-AIA group (Fig. 1b). Comparison of the concentrations of PGE<sub>2</sub> in the nasal polyps of the two patients groups (CRS-ATA and CRS-AIA) divided according to the type of BA associated with CRS (ATA



**Fig. 2** Correlation between the concentration of PGD<sub>2</sub> and the number of tryptase-positive cells (a), PGE<sub>2</sub> and the number of CD68-positive cells (b). Correlation analysis was performed using Spearman's rank correlation coefficient (●: CRA-NA, ○: CRS-ATA, △: CRS-AIA).



**Fig. 3** Balance among the PGD<sub>2</sub>, PGE<sub>2</sub>, CysLTs concentrations in the nasal polyps. PGD<sub>2</sub>/PGE<sub>2</sub> ratio (a), PGD<sub>2</sub>/CysLTs ratio (b) and PGE<sub>2</sub>/CysLTs ratio (c). Between-group comparisons were performed by Mann-Whitney's *U*-test with Bonferroni correction (\* $p < 0.05$ , \*\* $p < 0.01$ ).

and AIA, respectively) revealed that the concentration of PGE<sub>2</sub> was lower in the CRS-AIA group than in the CRS-ATA group ( $P = 0.024$ ).

The concentrations of CysLTs were significantly higher in the nasal polyps of the CRS-AIA group than in the control specimens ( $P = 0.037$ , Fig. 1c). The same parameter tended to be higher in the CRS-AIA group than in the CRS-ATA group, although this difference was not statistically significant.

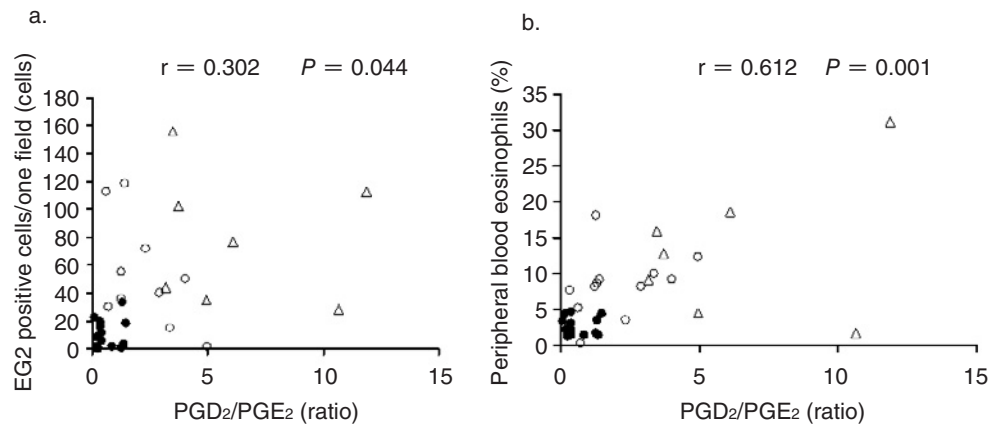
### EXPRESSION OF MAST CELL TRYPTASE AND CD68 IN THE NASAL POLYPS

Next, the mast cells and monocyte macrophages in the nasal polyps were counted by means of immunohistochemical staining and their counts were analyzed in relation to the levels of expression of the arachidonic acid metabolites (Fig. 2). The results revealed that the number of mast cell tryptase-positive cells was strongly correlated with the concentrations

of PGD<sub>2</sub> ( $r = 0.702$ ,  $P < 0.001$ ; Fig. 2a). According to the analysis in each group, the number of mast cell tryptase-positive cells was correlated with the concentrations of PGD<sub>2</sub> in the CRS-NA group ( $P < 0.001$ ) and the CRS-ATA group ( $P = 0.029$ ). The number of CD68-positive cells was correlated with the concentrations of PGE<sub>2</sub> in the nasal polyps ( $r = 0.294$ ,  $P = 0.048$ ; Fig. 2b). According to the analysis in each group, the number of CD68-positive cells was correlated with the concentrations of PGE<sub>2</sub> in the CRS-NA group ( $P = 0.044$ ).

### COMPARISON OF THE ARACHIDONIC ACID METABOLITES

The PGD<sub>2</sub>/PGE<sub>2</sub> ratio, serving as an indicator of the balance between PGD<sub>2</sub> and PGE<sub>2</sub>, was compared among the different groups (Fig. 3a). The PGD<sub>2</sub>/PGE<sub>2</sub> ratio was found to be the highest in the CRS-AIA group, followed by that in the CRS-ATA group,



**Fig. 4** Correlations between the PGD<sub>2</sub>/PGE<sub>2</sub> ratio and the number of EG2-positive cells (a) and the percentage of eosinophil in peripheral blood (b). Correlation analysis was performed using Spearman's rank correlation coefficient (●: CRA-NA, ○: CRS-ATA, △: CRS-AIA).

and lowest in the CRS-NA group. Furthermore, the PGD<sub>2</sub>/CysLTs ratio (serving as an indicator of the balance between PGD<sub>2</sub> and the CysLTs) and the PGE<sub>2</sub>/CysLTs ratio (serving as an indicator of the balance between PGE<sub>2</sub> and the CysLTs) were also compared among the different groups, as shown in Figure 3b, 3c, respectively. There was no significant difference in the PGD<sub>2</sub>/CysLTs ratio. On the other hand, the PGE<sub>2</sub>/CysLTs ratio was the highest in the CRS-NA group followed by that in the CRS-ATA group, and lowest in the CRS-AIA group.

#### COMPARISON OF THE PGD<sub>2</sub>/PGE<sub>2</sub> RATIO AND EOSINOPHILS IN THE NASAL POLYPS

Figure 4a shows the data concerning the correlation between the PGD<sub>2</sub>/PGE<sub>2</sub> ratio and the number of EG2-positive cells in the nasal polyps. The PGD<sub>2</sub>/PGE<sub>2</sub> ratio was positively correlated with the number of EG2-positive cells in the nasal polyps ( $r = 0.302$ ;  $P = 0.044$ ). According to analysis in each group, this ratio was not correlated with the number of EG2-positive cells in the nasal polyps although a tendency was observed. Figure 4b shows the data concerning the correlation between the PGD<sub>2</sub>/PGE<sub>2</sub> ratio and the differential eosinophil count in the peripheral blood. The PGD<sub>2</sub>/PGE<sub>2</sub> ratio was positively correlated with the peripheral blood differential eosinophil count ( $r = 0.612$ ;  $P = 0.001$ ). According to analyses in each group, this ratio was not correlated with the number of EG2-positive cells in the peripheral blood though a tendency was observed.

#### DISCUSSION

From the findings in this study, we provided evidence, for the first time, of a significant elevation of the concentration of PGD<sub>2</sub> in the nasal polyps of patients with CRS complicated by ATA (CRS-ATA). Furthermore, we found that the PGD<sub>2</sub>/PGE<sub>2</sub> ratio was

markedly elevated in the nasal polyps of patients with CRS complicated by AIA (CRS-AIA). Previous studies have reported a strong correlation between the severity of BA and the concentrations of PGD<sub>2</sub>.<sup>19,32,33</sup> In contrast, it is generally believed that CRS with BA is associated with a poor prognosis. Some reports have suggested that similar pathogenetic mechanisms might be involved in BA and CRS in patients with CRS complicated by BA.<sup>4-6,10</sup> Based on these observations, we analyzed the PGD<sub>2</sub> and PGE<sub>2</sub> concentrations in the nasal polyps of patients with intractable CRS complicated by BA.

The CRS patients from whom the nasal polyp specimens were collected were divided into three groups: (1) CRS-NA (CRS patients without BA), (2) CRS-ATA (CRS patients with complicating aspirin-tolerant (no aspirin sensitivity) asthma) and (3) CRS-AIA (CRS patients with complicating aspirin-intolerant (aspirin-sensitive) asthma). The PGD<sub>2</sub> concentrations were highest in the nasal polyps of the CRS-ATA group (Fig. 1a). This result endorses the view that there might be a close correlation between the pathophysiology of BA and PGD<sub>2</sub>, and suggests that PGD<sub>2</sub> might be involved in the intractable course of CRS. Based on this finding, we checked the expression of tryptase of mast cell origin in the nasal polyps by means of immunohistochemical analysis. This analysis revealed a positive correlation between the tryptase-positive cell count and the nasal polyp PGD<sub>2</sub> concentration (Fig. 2a). This finding suggested that PGD<sub>2</sub> production is elevated in nasal polyps showing intense mast cell infiltration. The PGD<sub>2</sub> concentration tended to be lower in the polyps of the CRS-AIA group than in those of the CRS-ATA group, although this difference was not statistically significant (Fig. 1 a). In previous reports, the pathogenesis of AIA was attributed to downregulation of cyclooxygenase (COX)-2, and it was shown that COX-2 downregula-

tion leads to an increase in the production of CysLTs and decrease in the production of PGE<sub>2</sub>.<sup>34-37</sup> In the present study also, significantly lower PGE<sub>2</sub> concentrations (Fig. 1b) and significantly higher CysLTs concentrations (Fig. 1c) were found in the polyps of the CRS-AIA group. We may therefore estimate that COX-2 downregulation is responsible for the reduction of the PGD<sub>2</sub> concentrations in the nasal polyps of patients with CRS-AIA. When the correlation of the PGE<sub>2</sub> with the number of infiltrating cells as determined by immunohistochemical analysis was examined, a positive correlation was noted between the PGE<sub>2</sub> concentration and the CD68-positive cell count (Fig. 2b). On the basis of these results, we may estimate that the PGE<sub>2</sub> production is primarily undertaken by macrophages.

It has recently been reported that the PGD<sub>2</sub>/PGE<sub>2</sub> balance is closely involved in various inflammatory conditions.<sup>28,29,38</sup> In the present study also, the PGD<sub>2</sub>/PGE<sub>2</sub> ratio was in the order of CRS-AIA group > CRS-ATA group > CRS-NA group (Fig. 3a). That is, this ratio was higher in cases with intractable CRS that was considered to be likely to be characterized by repeated cycles of remission and relapse (e.g., CRA-AIA and CRS-ATA). Furthermore, a positive correlation was noted between the PGD<sub>2</sub>/PGE<sub>2</sub> ratio and the nasal polyp EG2-positive cell count (Fig. 4a) and between the PGD<sub>2</sub>/PGE<sub>2</sub> ratio and the percentage of eosinophils in the peripheral blood (Fig. 4b), suggesting that the PGD<sub>2</sub>/PGE<sub>2</sub> ratio may serve as an indicator of the severity of CRS, as is the case with tissue and peripheral eosinophil counts. However, it is unclear why this ratio correlated with the percentage of eosinophils in the peripheral blood. In previous reports, PGD<sub>2</sub> induced the rapid release of eosinophils from bone marrow though PGE<sub>2</sub> induced apoptosis in developing eosinophils through inducible nitric oxide synthase (NOS) and inhibited the responses of bone-marrow myeloid progenitors to GM-CSF and of eosinophil precursors to IL-5.<sup>39-41</sup> We considered that high PGD<sub>2</sub> and low PGE<sub>2</sub> levels might increase eosinophils in the peripheral blood accordingly. In this connection, Pierzchalska *et al.*<sup>42</sup> reported a study involving stimulation of fibroblasts (cultured after collection from bronchial biopsy specimens) with IL-1β, TNF-α or LPS and analysis of the expression of PGE<sub>2</sub> and PGD<sub>2</sub> in vitro, in which they demonstrated that the PGE<sub>2</sub>/PGD<sub>2</sub> ratio was significantly lower in these fibroblasts as compared with those in the fibroblasts isolated from non-asthmatic patients. In contrast to the design of their study, our study was designed to quantify the expression of PGD<sub>2</sub> and PGE<sub>2</sub> throughout all tissues containing cells capable of producing them. Therefore, the data from this study may be viewed as reflecting clinical cases more faithfully. Regarding the pathophysiology of CRS, Okano *et al.*<sup>30</sup> analyzed the nasal polyp levels of PGD<sub>2</sub> synthase (PGDS) and PGE<sub>2</sub> synthase (PGES) in patients with

CRS, based on the contention that an increase in PGD<sub>2</sub> and decrease in PGE<sub>2</sub> can aggravate eosinophil-induced airway inflammation. Our study differs from theirs in that our study involved the quantification of arachidonic acid metabolites in the nasal polyps by EIA instead of analysis of the respective syntheses. Furthermore, by dividing CRS complicated by asthma into two types (a type with aspirin sensitivity and a type without aspirin sensitivity), the present study demonstrated a closer correlation of the PGD<sub>2</sub>/PGE<sub>2</sub> ratio with CRS-AIA (CRS complicated by asthma with aspirin sensitivity) than with CRS-ATA. Furthermore, both the PGD<sub>2</sub>/CysLTs ratio (Fig. 3b) and the PGE<sub>2</sub>/CysLTs ratio (Fig. 3c) were lower in the CRS-AIA group than in the CRS-ATA group. These results seem to be attributable to the greater downregulation of COX-2 in these cases, as described above.

In the analysis of the association with predisposition to allergy, no significant correlation was noted between the PGD<sub>2</sub>/PGE<sub>2</sub> ratio and the serum total IgE level (data not shown). These results suggest that the PGD<sub>2</sub>/PGE<sub>2</sub> ratio may be independent of atopic status.

Some investigators reported that paranasal sinus CT scans tend to reveal more severe lesions in cases of CRS with intense eosinophil infiltration (e.g., cases of CRS-ATA and CRS-AIA).<sup>43</sup> If this previous finding is taken into consideration with the results of the present study, it seems likely that the PGD<sub>2</sub>/PGE<sub>2</sub> ratio correlates positively with the radiological severity of CRS. In the previous report, a significant positive correlation was noted between the haemopoietic-type PGDS (h-PGDS) levels and the radiological severity of sinusitis, while a significant inverse correlation was noted between the microsomal PGES-1 (m-PGES-1) levels and the severity.<sup>30</sup> However, the PGD<sub>2</sub>/PGE<sub>2</sub> ratio were not correlated with radiological severity of sinusitis in this study (*P* = 0.189; data not shown). One possible reason for this finding is that in cases with intense eosinophil infiltration (e.g., CRS-AIA group and CRS-ATA group), lesions are often confined to the ethmoid sinus or the surrounding area and the CT score is not always high.

In conclusion, the concentrations of the PGD<sub>2</sub> were significantly higher in the polyps obtained from patients with CRS-ATA as compared with those in the control specimens. The concentrations of PGE<sub>2</sub> were highest in the control specimens, followed by those in the CRS-ATA group, and lowest in the CRS-AIA group. The PGD<sub>2</sub>/PGE<sub>2</sub> ratio was highest in the CRS-AIA group, followed by that in the CRS-ATA group, and lowest in the CRS-NA group. These findings suggest that the PGD<sub>2</sub>/PGE<sub>2</sub> ratio may be an indicator of the severity of CRS as one of the alternatives to the eosinophilic infiltration. Clinically, CRS complicated by AIA is known to be characterized by repeated cycles of remission and relapse and to be highly intrac-

table. Because such cases had the highest nasal polyp PGD<sub>2</sub>/PGE<sub>2</sub> ratio in the present study, we may say that the PGD<sub>2</sub>/PGE<sub>2</sub> ratio reflects the intractable nature of CRS very well. Treatment of intractable CRS may be possible if the increase of PGD<sub>2</sub> and decrease of PGE<sub>2</sub> in such cases can be controlled.

## ACKNOWLEDGEMENTS

We thank Ms. Hiromi Katsuyama and Ms. Nao Aida of the Jikei University School of Medicine for their skillful technical assistance. This study was supported by a research fund from the Taiho Pharmaceutical Co, Ltd., Japan.

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