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Letter to the Editor

Effect of endoscopic sinus surgery for chronic rhinosinusitis on the state of coexisting asthma

Dear Editor,

Chronic rhinosinusitis (CRS) and asthma frequently coexist and are associated with each other. The prevalence of asthma in patients with CRS has been reported to be 4%–44%,^{1,2} and CRS is more severe in patients with coexisting asthma than in those without.³ CRS is a heterogeneous disease, and is classified based on the presence (CRSwNP) or absence (CRSSNP) of nasal polyps.⁴ CRSwNP is characterized by Th2-skewed eosinophilic inflammation, whereas CRSSNP predominantly comprises of a Th1 milieu.^{5,6} Eosinophilic CRS (ECRS) is one of the endotypes of CRSwNP with strong eosinophilic infiltration, and often coexists with asthma, increases its severity, and is refractory to medical treatment.⁶ Based on the united-airways concept, endoscopic sinus surgery (ESS) for CRS is expected to show a positive effect on the state of coexisting asthma. However, a previous meta-analysis⁷ showed beneficial effects of ESS on asthma control, asthma exacerbation frequency, and oral corticosteroid usage, but not pulmonary function. The aim of this study was to evaluate the effect of ESS on the state of coexisting asthma in all CRS patients with asthma, and to compare the effect between two patient subgroups: ECRS patients with asthma and non-ECRS patients with asthma.

In this retrospective study, we enrolled adult patients with CRS with or without asthma, who underwent conventional ESS at Takatsuki Red Cross Hospital from January 2010 to December 2016. Postoperatively, all patients were treated with a macrolide antibiotic and a topical glucocorticosteroid. They were classified into two subgroups: ECRS and non-ECRS, based on the Japan Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis score (≥ 11) and the number of eosinophils in the submucosa of the ethmoid cavity or nasal polyps (≥ 70 /high-power field).⁶ This study was approved by the ethics committee of Takatsuki Red Cross Hospital (H29-41).

The prevalence of coexisting asthma in all CRS patients and the two patient subgroups (ECRS and non-ECRS) was evaluated. The effect of ESS for CRS on coexisting asthma was evaluated in all CRS patients with asthma. The following parameters were assessed: changes in asthma exacerbation frequency requiring systemic corticosteroids for at least 3 days during 6 months before and after ESS; changes in anti-asthma medication (dosage of inhaled corticosteroids [ICS] and number of controller medications); and pulmonary function (forced vital capacity [FVC] [%predicted], FEV₁ [%predicted], and forced expiratory flow at 25%–75% [FEF_{25–75}] [%predicted]) from baseline to 6 months after ESS. Subsequently,

the same variables were compared between two patient subgroups: ECRS patients with asthma and non-ECRS patients with asthma. Finally, factors associated with the effectiveness of ESS on the state of coexisting asthma were assessed. We dichotomized patients with CRS and asthma into two subgroups: responders and non-responders. Patients were defined as responders if they demonstrated a decrease in asthma exacerbation frequency, anti-asthma medication, or an improvement in pulmonary function after ESS. JMP system version 14 (SAS Institute Japan, Tokyo, Japan) was used for statistical analyses.

Of 187 patients with CRS (66 females; age, 52.1 ± 15.8 years), 69 (36.9%) had coexisting asthma. The prevalence of coexisting asthma was significantly higher in ECRS patients than in non-ECRS patients (47.5% vs. 29.0%, $p = 0.0009$). These results are consistent with those of previous studies.^{1,2} Of the 69 patients with CRS and asthma, there was no significant difference in the demographic characteristics between 38 ECRS patients with asthma and 31 non-ECRS patients with asthma, with the exception of blood eosinophil proportion (Table 1). In the 69 patients with CRS and asthma, the asthma exacerbation frequency, ICS dosage, and number of controller medications significantly decreased before and after ESS, although, there was no significant change in pulmonary function (Table 2). This result is consistent with the previous meta-analysis.⁷ CRS consists of several phenotypes or inflammatory endotypes, and postoperative CRS outcomes differs among these.⁸ In ECRS patients with asthma, the dosage of ICS significantly decreased before and after ESS (Table 2). Meanwhile, in non-ECRS patients with asthma, the asthma exacerbation frequency, ICS dosage, and number of controller medications significantly decreased, and FEV₁ (%predicted) increased before and after ESS (Table 2). The beneficial effect of ESS on coexisting asthma was more evident in non-ECRS patients than in ECRS patients in terms of the three variables listed in Table 2. To clarify the factors associated with the effectiveness of ESS on the state of coexisting asthma, we performed multivariate logistic regression analysis. Of the 69 patients with CRS and coexisting asthma, 39 were responders. Univariate analysis identified three statistically significant factors for the effectiveness of ESS on the state of coexisting asthma: age, no history of ESS, and non-ECRS. Multivariate logistic regression analysis showed that age (OR = 1.06; 95% CIs, 1.01–1.13; $p = 0.03$), no history of ESS (OR = 17.87; 95% CIs, 1.54–206.75, $p = 0.02$), and non-ECRS (OR = 10.49 95% CIs, 1.06–103.48; $p = 0.04$) were independently associated with the effectiveness of ESS on the state of coexisting asthma. These results also showed that non-ECRS was an independent factor for the effectiveness of ESS on the state of coexisting asthma. Tissue eosinophilic inflammation in the upper

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Table 1
Demographic characteristics of ECRS and non-ECRS patients with asthma.

	ECRS with asthma (n = 38)	Non-ECRS with asthma (n = 31)	p-value [*]
Age, years	52.2 ± 15.5	51.0 ± 16.4	0.89
Sex, male/female	17/21	17/14	0.40
Previous history of ESS, yes	5 (13.2)	2 (6.5)	0.36
CRS onset, years	45.7 ± 18.2	49.1 ± 17.0	0.36
Asthma onset, years	38.8 ± 21.6	35.3 ± 23.4	0.58
Asthma exacerbations [†] , times	0 (0–3)	0 (0–2)	0.62
Doses of ICS, µg/daily [‡]	536.8 ± 314.9	422.6 ± 286.0	0.12
Number of controller medications	2 (0–3)	1 (0–3)	0.11
Blood eosinophils, %	8.4 ± 4.5	6.3 ± 4.4	0.02
Spirometry			
FVC (%predicted), %	105.9 ± 20.8	108.5 ± 10.6	0.21
FEV ₁ (%predicted), %	94.2 ± 17.5	97.3 ± 16.2	0.37
FEF25–75 (%predicted), %	63.5 ± 30.6	66.5 ± 33.5	0.73

Values are presented as mean ± SD, median (range), or number (%).

CRS, chronic rhinosinusitis; ECRS, eosinophilic CRS; ESS, endoscopic sinus surgery; FVC, forced vital capacity; FEF25–75, forced expiratory flow at 25%–75%; CT, computed tomography.

^{*} By Wilcoxon rank-sum test or chi-squared test.

[†] Required systemic corticosteroids for at least 3 days during 6 months before ESS.

[‡] Equivalent to fluticasone propionate.

Table 2
Effect of ESS for CRS on the state of coexisting asthma.

	Baseline	6 months after ESS	p-value [*]
All patients with CRS with asthma (n = 69)			
Asthma exacerbations [†] , times	0 (0–3)	0 (0–2)	0.04
Doses of ICS [‡] , µg/day	485.5 ± 305.5	361.2 ± 272.9	<0.0001
Number of controller medications	1 (0–3)	1 (0–3)	0.008
FVC (%predicted), %	107.1 ± 16.9	110.5 ± 16.0	0.07
FEV ₁ (%predicted), %	95.6 ± 16.9	98.4 ± 16.7	0.11
FEF25–75 (%predicted), %	64.9 ± 31.7	63.2 ± 29.8	0.77
Patients with ECRS with asthma (n = 38)			
Asthma exacerbations [†] , times	0 (0–3)	0 (0–2)	0.34
Doses of ICS [‡] , µg/day	536.8 ± 314.9	398.5 ± 283.5	0.002
Number of controller medications	2 (0–3)	1 (0–3)	0.18
FVC (%predicted), %	105.9 ± 20.8	110.9 ± 17.7	0.18
FEV ₁ (%predicted), %	94.2 ± 17.5	97.6 ± 18.7	0.95
FEF25–75 (%predicted), %	63.5 ± 30.6	62.7 ± 32.3	0.29
Patients with non-ECRS with asthma (n = 31)			
Asthma exacerbations [†] , times	0 (0–2)	0 (0–0)	0.04
Doses of ICS [‡] , µg/day	422.6 ± 286.0	312.0 ± 255.5	0.003
Number of controller medications	1 (0–3)	1 (0–2)	0.03
FVC (%predicted), %	108.5 ± 10.6	109.9 ± 13.5	0.27
FEV ₁ (%predicted), %	97.3 ± 16.2	99.5 ± 13.6	0.03
FEF25–75 (%predicted), %	66.5 ± 33.5	63.9 ± 26.5	0.32

Values are presented as means ± SD or median (range).

ESS, endoscopic sinus surgery; CRS, chronic rhinosinusitis; FVC, forced vital capacity; FEF25–75, forced expiratory flow at 25%–75%.

^{*} By Wilcoxon rank-sum test.

[†] Required systemic corticosteroids for at least 3 days during 6 months before or after ESS.

[‡] Equivalent to fluticasone propionate.

airway may also play a pivotal role in determining the postoperative lower airway outcomes.

Among all patients with CRS, those with eosinophilic⁸ or type 2 inflammation-dominant⁹ CRSwNP showed the highest polyp recurrence after ESS. Tissue eosinophilic inflammation appeared to correlate with postoperative CRS outcomes. The correlation between phenotypes or inflammatory endotypes of CRS with the postoperative state of coexisting asthma has only been reported in one study.¹⁰ The study showed significantly improved pulmonary function after

ESS in aspirin-tolerant patients, but not in aspirin-sensitive patients. Therefore, we compared the effect of ESS on coexisting asthma between two patient subgroups.

This study has some limitations. It is a retrospective study with a small sample size. However, as a single-center study, the same otolaryngologist (S.F.) performed ESS in all the patients. The surgical procedures were constant.

In conclusion, ESS for CRS has a beneficial effect on the state of coexisting asthma in CRS patients with asthma. This effect may be more evident in non-ECRS patients than in ECRS patients.

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Conflict of interest

The authors have no conflict of interest to declare.

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