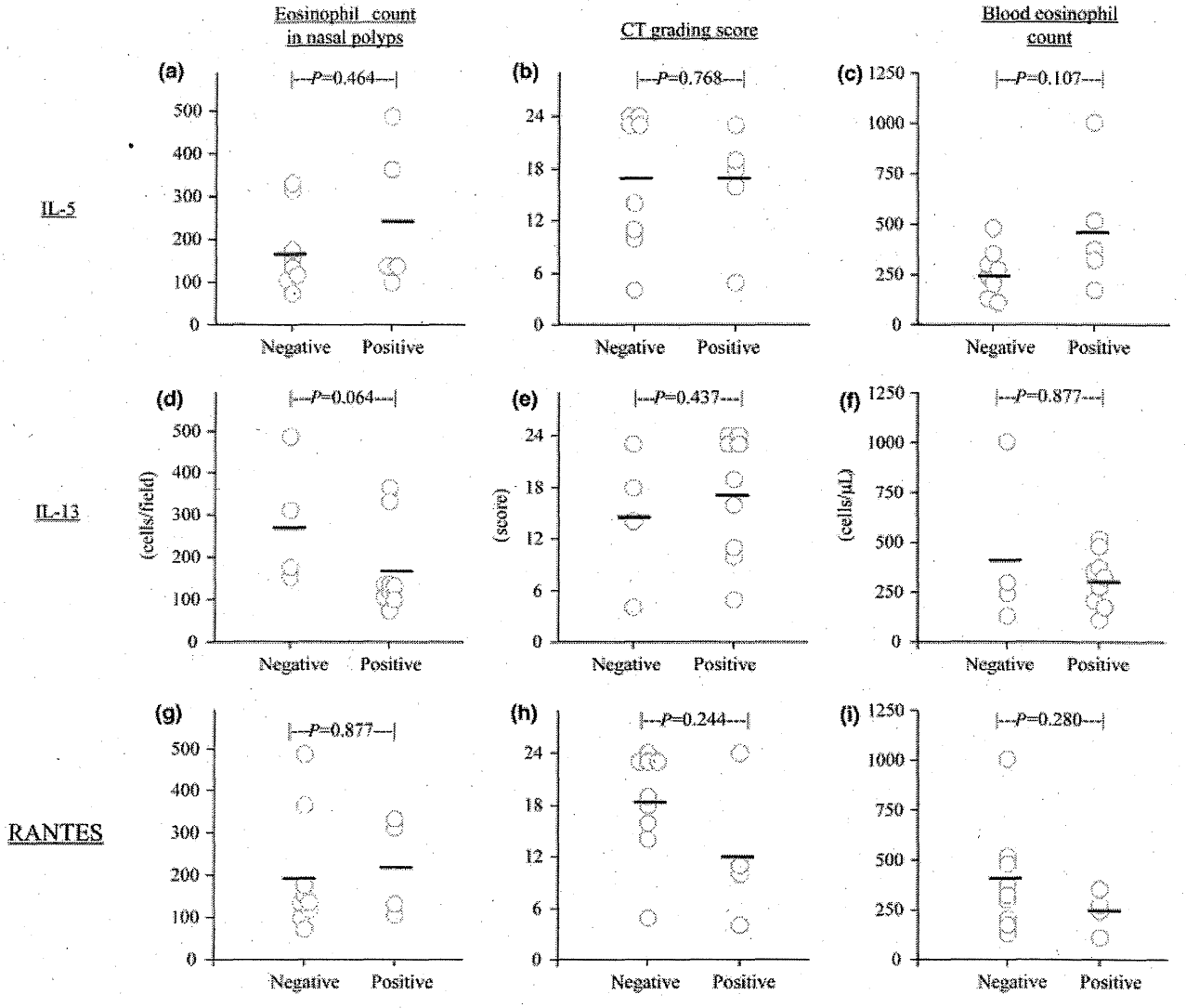

Fig. 3. Comparison of nasal polyp eosinophilia (a, d, g), radiological severity of sinusitis (b, e, h) and blood eosinophil count (c, f, i) between patients with positive and negative response of IL-5 (a–c), IL-13 (d–f) and RANTES (g–i) production in response to 200 μg/mL of *Aspergillus* in dispersed nasal polyp cells. Bars represent as a mean. *P*-value was obtained through the use of Mann–Whitney's *U*-test.

was tested. Because little is known whether *Candida* plays a role in the cellular responses in CRSwNP as compared with *Aspergillus* and *Alternaria*, we firstly set *Candida* as a control for other fungi. Surprisingly, *Candida* evoked IL-5 and IL-13 production similar to *Aspergillus* and *Alternaria*.

In conclusion, we present here *ex vivo* functional evidence that, although DNPCs can respond to fungal extracts resulting in the production of eosinophilia-associated cytokines especially IL-5 and IL-13, these responses are significantly less than those induced by SEB. These observations suggest a role for SEB in promoting eosinophilic infiltration and may provide a basis for therapeutic approaches for targeting microorganisms in the management of CRSwNP.

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ORIGINAL CONTRIBUTION

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Mucosal eosinophilia and recurrence of nasal polyps – new classification of chronic rhinosinusitis*

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SUMMARY

Background: *Eosinophils and nasal polyps are believed to affect the surgical outcome of chronic rhinosinusitis (CRS). CRS is classified based on the presence of nasal polyps in western countries. The majority of patients with CRS with nasal polyps (CRS with NP) are characterized by predominantly eosinophilic inflammation. However, Asian patients with CRS with NP show characteristics indicative of neutrophilic inflammation. Therefore, are eosinophils or nasal polyps more important for the classification of CRS?*

Methods: *A prospective cohort study conducted from April 2007 to March 2008 classified patients with CRS based on the presence of nasal polyps and mucosal eosinophilia. The recurrence rate of nasal polyps was compared between the groups. Recurrence rate was analysed as a time-dependent variable by the Kaplan-Meier method.*

Results: *Eosinophilic inflammation was found in 59.6% of patients with CRS with NP. Patients with mucosal eosinophilia had higher polyp recurrence rate than patients without mucosal eosinophilia, whereas patients with nasal polyps did not have higher polyp recurrence rate than patients without nasal polyps.*

Conclusions: *Presence of mucosal eosinophilia is a more important factor than nasal polyps for classifying CRS in terms of the surgical outcome.*

Key words: chronic rhinosinusitis, eosinophils, nasal polyps, endoscopic sinus surgery, recurrence

INTRODUCTION

Chronic rhinosinusitis (CRS) is one of the most common chronic diseases, but little is understood about its pathogenesis. CRS is usually classified based on the presence or absence of nasal polyps [1,2]. The presence of nasal polyps indicates refractory disease with a tendency to recur, often requiring long-term medical therapy despite successful surgical intervention [3-5]. Mucosal eosinophilia is also widely reported as a marker of inflammation in patients with CRS [6]. The presence of mucosal eosinophilia is frequently associated with more severe disease and recurrence of nasal polyps after surgery [7]. However, nasal polyps do not show the same eosinophilic inflammatory pattern in different parts of the world [8]. Eosinophilic inflammation is found in about 80% of cases of CRS with nasal polyps (CRS with NP) in western countries [9]. In contrast, neutrophilic inflammation is common in cases of CRS with NP in Asia, such as south Chinese and Korean patients [10,11]. Such findings raise the question of which characteristic is more important for the classification of CRS, the presence of eosinophils or nasal polyps?

The present study investigated the effect of mucosal eosinophilia and nasal polyps on the recurrence rate of nasal polyps and the importance of these characteristics for the classification of CRS.

METHODS

Subjects

This prospective study enrolled 223 patients with CRS from April 2007 to March 2008. The diagnosis of sinus disease was based on patient history, clinical examination, nasal endoscopy, and computed tomography (CT) of the sinuses according to the guidelines of the European Position Paper on Rhinosinusitis and Nasal Polyps [1]. This study excluded patients treated with oral steroid or antimicrobial agents within 4 weeks before surgery, and patients with unilateral disease, fungal disease, antrochoanal polyps, and cyst of the paranasal sinuses. Preoperative demographic and medical history was obtained from the patient, including age, sex, history of prior sinus surgery, smoking habit, asthma, and allergic rhinitis. Allergic rhinitis was confirmed by intradermal skin testing, and

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serum total immunoglobulin E (IgE) and specific IgE for common allergen were measured by fluoroenzyme immunoassay. CT findings were graded according to the Lund-MacKay method [12]. All patients followed up for at least 6 months were included in the analysis. Polyps were graded using the 0 - 3 scoring system recommended by the guidelines: score 0, absence of polyps; score 1, polyps in middle meatus only; score 2, polyps beyond the middle meatus but not blocking the nose completely; score 3, polyps completely obstructing the nose [1]. Recurrence of CRS was defined as the presence of nasal polyps detected by nasal endoscopy. The study was approved by the ethics committee of Jikei University School of Medicine.

Symptom scores

All participants were assessed before surgery regarding 5 symptoms; nasal obstruction, anterior nasal drainage, posterior nasal drainage, facial pain, and decreased sense of smell. The severity of each symptom was evaluated according to the 7-point (score 0 - 6) Likert scale. Total symptom score was calculated as the total of the 5 symptom scores.

CRS subgroups

Patients with CRS were classified on the basis of the presence of nasal polyps and histological detection of mucosal eosinophilia as defined by the eosinophil cut point into the following groups: eosinophilic CRS with nasal polyps (ECRS with NP), eosinophilic CRS without nasal polyps (ECRS without NP), non-eosinophilic CRS with nasal polyps (NECRS with NP), and non-eosinophilic CRS without nasal polyps (NECRS without NP). The recurrence of nasal polyps in these groups was investigated after endoscopic sinus surgery.

Histological analysis

Mucosal tissues of patients with CRS were removed from the nasal polyps or mucosa of the ethmoid cavity at the time of surgery. The tissue was fixed immediately in 10% formalin, embedded in paraffin, and cut into thin sections. The sections were stained with hematoxylin-eosin stain. The number of eosinophils in the mucosa was counted under high-power field (HPF, × 400) in which eosinophils were the densest cellular infiltrate beneath the epithelial surface. Histological examinations were performed by three physicians unaware of the clinical data, and the mean number of eosinophils was calculated.

Statistics

The eosinophil cut off point was determined from the relationship between the eosinophil count and polyp recurrence using the univariate Cox proportional hazards model and the area under the receiver operating characteristic curve (AUC). The optimal cut off point was defined with the minimum corresponding p-value and the maximum AUC. Patients with eosinophil count above the cut off point were considered to have mucosal eosinophilia. The analysis of variance test was used to evaluate differences in patient characteristics between the subgroups. Disease-free survival curves were drawn using the Kaplan-Meier method and compared using the log-rank test. Disease-free survival was defined as the time that the patient remained without nasal polyps after endoscopic sinus surgery. Cox proportional hazard models were fitted for subgroups and parameters, and hazard ratio (HR) and 95% confidence intervals (CI) were calculated. All statistical analyses were performed using STATA 9.1 (STATA Corp, College Station, TX, USA). A value of $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 175 of the 223 enrolled patients (78.5%) had adequate data for analyses. The 129 male and 46 female patients were aged 19 to 77 years (mean 48.1 years). The mean follow-up period was 17.5 months. Twenty-one (12.0%) of these patients had asthma, 90 (51.4%) had allergic rhinitis, and 50 (28.6%) were current smokers. Forty patients (22.9%) suffered polyp recurrence after surgery during the follow-up period.

Eosinophil cut off point

The associations between eosinophil count and polyp recurrence are shown in Figure 1. Patients with ≥ 60 and ≥ 70 eosinophils/HPF showed the minimum p values ($p = 0.001$) and patients with ≥ 70 eosinophils/HPF showed the highest AUC (0.673). Therefore, mucosal eosinophilia was defined as ≥ 70 eosinophils/HPF.

CRS subgroups

Clinical characteristics of each classification are summarized in Table 1. More than half (59.6%) of the patients with CRS with NP had mucosal eosinophilia. The numbers of patients with allergic rhinitis ($p = 0.019$), asthma ($p = 0.001$), current smoker ($p = 0.032$), and total symptom score ($p = 0.005$) were significantly different between the 4 groups. The number of patients with polyp recurrence was also significantly different between these groups ($p = 0.001$).

Prognostic factors

Patients with mucosal eosinophilia (70/HPF and over) had a poor prognosis (HR: 3.47; 95% CI: 1.65-7.29; $p = 0.001$). Asthma ($p = 0.000$), polyp score ($p = 0.001$), CT score ($p = 0.001$), and allergic rhinitis ($p = 0.026$) were also predictors of recurrence by univariate analysis using the Cox proportional model (Table 2). The real eosinophil numbers were not correlated with recurrence (HR: 1.001; 95% CI: 0.99-1.00; $p = 0.164$).

Recurrence rate

Patients with mucosal eosinophilia had a significantly higher polyp recurrence rate by log-rank test ($p = 0.0005$) (Figure 2A). However, patients with nasal polyps did not have a significantly higher polyp recurrence rate than patients without nasal polyps ($p = 0.0535$) (Figure 2B). Regardless of the presence or absence of nasal polyps, patients with mucosal eosi-

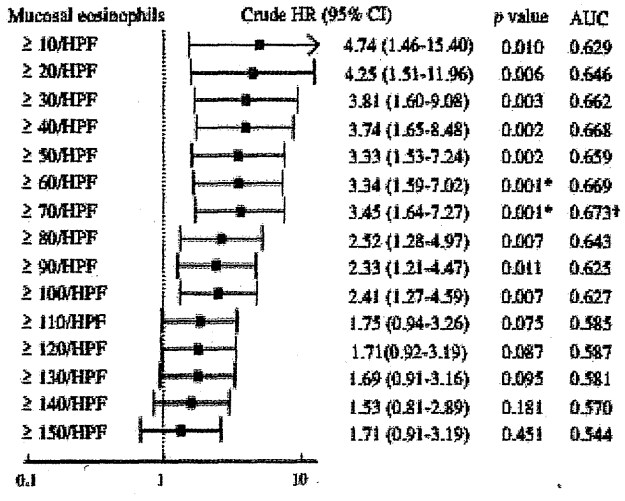

Figure 1. Association of mucosal eosinophils with polyp recurrence. HR = hazard ratio, CI = confidence interval. * Minimum p value, †highest AUC.

nophilia had a significantly higher recurrence rate (p = 0.0067) among the 4 groups (Figure 2C). Investigation of disease-free survival in the 4 groups showed that patients with NECRS with NP (HR, 0.27; 95% CI, 0.10-0.72; p = 0.008) and NECRS without NP (HR, 0.24; 95% CI, 0.10-0.72; p = 0.007) had better prognosis than patients with ECRS with NP. Patients with ECRS without NP (HR, 0.55; 95% CI, 0.21-1.44; p = 0.225) did not have better survival than patients with ECRS with NP (Table 3). These findings indicate that the presence of mucosal eosinophilia is more important than nasal polyps in the recurrence of CRS.

DISCUSSION

The present study found that more than half (59.6%) of Japanese patients with CRS with NP had mucosal eosinophilia. Histologically, CRS with NP is believed to be characterized by predominantly eosinophilic inflammation, whereas CRS without NP is characterized by neutrophilic inflammation with a lesser contribution of eosinophils [1,2]. Eosinophilic inflammation has been reported in 80% of patients with CRS with NP [9], suggesting that CRS with NP is equivalent to CRS with mucosal eosinophilia. However, mucosal eosinophilia was present in 46.4% of patients with CRS with NP versus 12% of patients with CRS without NP in south China [10]. Moreover, eosinophilic inflammation was found only in 33.3% of 30 patients in Korea [11]. Therefore, NPs are not associated with the same eosinophilic inflammatory patterns in different parts of the world [8]. This study showed that the prevalence of mucosal eosinophilia in Japanese patients with CRS with NP was intermediate between the prevalences reported in western countries and other eastern Asian countries.

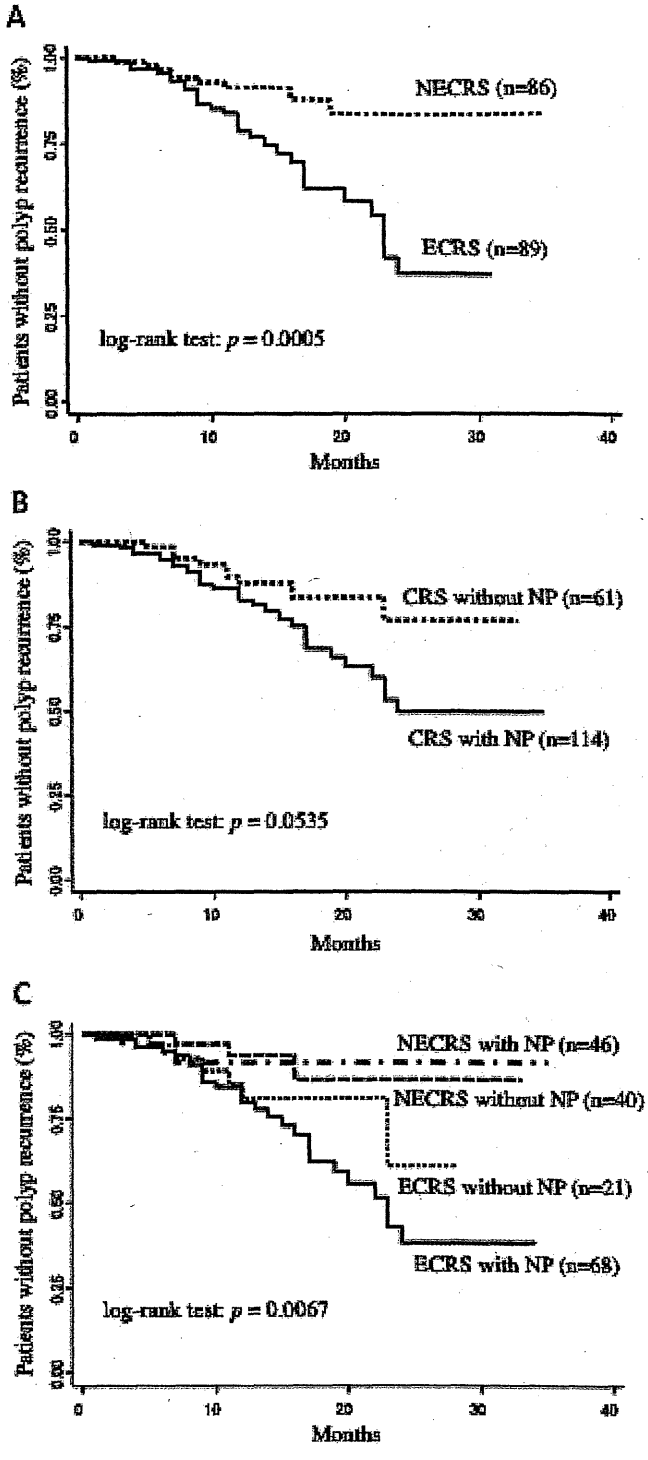

Figure 2. Kaplan-Meier curves of disease-free survival rates in patients with CRS. (A) Survival of patients with mucosal eosinophilia (ECRS) (solid line) exceeded survival of patients without mucosal eosinophilia (NECRS) (dashed line). (B) Survival of patients with nasal polyps (CRS with NP) (solid line) exceeded survival of patients without nasal polyps (CRS without NP) (dashed line), not significant. (C) Survival of patients with mucosal eosinophilia (ECRS with NP and ECRS without NP) exceeded survival of patients without mucosal eosinophilia.

The presence of mucosal eosinophilia is frequently associated with more severe disease and recurrence of nasal polyps after surgery [7]. Several studies have investigated the relationship between the number of mucosal eosinophils and surgical

Table 1. Patient characteristics. Level of significance (p) obtained by analysis of variance.

	ECRS with NP (n=68)	ECRS without NP (n=21)	NECRS with NP (n=46)	NECRS without NP (n=40)	p value
Sex, female/male	17/51	6/15	11/35	12/28	0.912
Age, mean ± SE (y)	48.2±13.3	42.6±12.4	51.1±16.8	47.5±14.3	0.172
Previous surgery	14/68	2/21	10/46	8/40	0.679
Allergic rhinitis	43/68	13/21	17/46	17/40	0.019
Asthma	16/68	3/21	2/46	0/40	0.001
IgE (IU/ml)	277.6 ± 364.6	179.5 ± 315.4	178.9 ± 358.8	132.0 ± 149.1	0.131
CT score	14.09 ± 5.97	9.00 ± 3.38	13.09 ± 5.49	7.65 ± 3.48	0.000
Polyp score	4.00 ± 1.58	0.62 ± 0.67	3.59 ± 1.47	0.78 ± 0.89	0.000
Current smoker	20/68	1/21	13/46	16/40	0.032
TSS	15.22 ± 5.12	13.81 ± 7.06	14.57 ± 7.11	10.85 ± 6.08	0.005
Follow up (m)	18.07 ± 8.01	18.62 ± 7.71	16.72 ± 8.61	16.80 ± 7.23	0.679
Polyp recurrence	26/68	5/21	5/46	4/40	0.001

TSS = total symptom score.

Table 2. Cox proportional hazard models.

Variable	Crude HR	95% CI	p value
≥ 70 eosinophils/HPF	3.47	1.65-7.29	0.001*
Polyp score	1.30	1.12-1.52	0.001*
Asthma	3.26	1.69-6.26	0.000*
Allergic rhinitis	2.15	1.09-4.24	0.026*
CT score	1.09	1.03-1.15	0.001*
Prior sinus surgery	1.09	0.50-2.38	0.819
Current smoker	0.53	0.23-1.20	0.127
TSS	1.04	0.99-1.09	0.149
Age	0.99	0.48-1.90	0.915
Male	0.96	0.43-2.45	0.951

*p value is significant. HR = hazard ratio, CI = confidence interval, TSS = total symptom score.

Table 3. Cox proportional hazard model.

Variable	Crude HR	95% CI	p value
ECRS with NP	Reference	–	1.000
ECRS without NP	0.553	0.212 – 1.440	0.225
NECRS with NP	0.274	0.104 – 0.715	0.008*
NECRS without NP	0.235	0.082 – 0.674	0.007*

*p value is significant. HR = hazard ratio, CI = confidence interval, TSS = total symptom score.

outcomes, but few studies have considered the level of tissue eosinophil density required to define mucosal eosinophilia. Mucosal eosinophilia was defined as > 10 eosinophils/HPF and patients with eosinophilia showed significantly less improvement in quality-of-life outcomes [13]. Mucosal eosinophilia was also defined as more than 5 eosinophils/HPF and patients with mucosal eosinophilia had higher postoperative endoscopy scores [14]. The present study found that levels of mucosal eosinophil infiltrate of ≥ 70/HPF had the greatest impact on surgical outcome. Therefore, we defined mucosal eosinophilia as ≥ 70 eosinophils/HPF. However, this cut off point for eosinophil concentration does not specify the patient population with CRS. Patients with asthma are often treated with steroids before sinus surgery, and such medical intervention affects mucosal inflammation, including the degree of mucosal eosinophilia. Therefore, we excluded patients treated with oral steroids. Consequently, the real cut off point may be higher than 70 eosinophils/HPF.

In this study, patients with CRS with NP tended to show higher polyp recurrence than patients with CRS without NP, but not reaching statistical significance. In contrast, patients with CRS with mucosal eosinophilia showed significantly higher polyp recurrence. Therefore, we considered that eosinophils

are central in the pathogenesis of CRS. The pathophysiology of CRS with NP shows many differences from that of CRS without NP in western countries [1,2]. Mucosal eosinophilia is a characteristic of nasal polyps, but not of CRS without NP. However, we found that mucosal eosinophilia is also a key prognostic factor of CRS without NP. Interestingly, although patients with ECRS without NP did not have nasal polyps at the time of surgery, they showeda high polyp recurrence rate in the postoperative period. These findings suggest that eosinophilic CRS with NP and eosinophilic CRS without NP might be interpreted as different degrees of inflammation, and moreover may actually be the same disease entity. On the other hand, patients with non-eosinophilic with NP did not have a high polyp recurrence rate. In Chinese, CRS without NP and non-eosinophilic CRS with NP share a number of similarities in granulocyte activation and Th cell responses [10], indicating that non-eosinophilic CRS with NP and non-eosinophilic CRS without NP may be the same disease entity.

CRS with NP is equivalent to CRS with mucosal eosinophilia in western countries. Therefore, CRS with NP has been considered to have a high polyp recurrence. In fact, the initial stage of sinonasal polyposis did not correlate with recurrence after surgery or long-term outcomes in the European population [15]. Distinct mechanisms have not been considered to underlie the pathogenesis of NPs in these regions.

The present study indicates that mucosal eosinophilia is a more important prognostic factor than the presence of nasal polyps in terms of the surgical outcome. Consequently, we conclude that mucosal eosinophilia is a more important factor for classifying CRS than nasal polyps.

AUTHOR CONTRIBUTIONS

TN: data collection, analysis, writer; MY: study design, data collection; DA: study design, data collection; TO: study design, data collection; YM: study design, data collection; NO: study design, data collection; TH: statistical analysis; HM: conduct

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interest, financial or otherwise.

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臨　床

好酸球性副鼻腔炎における再手術後の自覚症状についての検討

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慢性副鼻腔炎に対し手術治療を行っても，炎症病態が再燃し再手術に至る症例は少なからず存在する。その中でも治癒寛解が困難な病態をもち，手術を行っても再発を繰り返すことが多い好酸球性副鼻腔炎と呼ばれる病態が近年問題となっている。そこで，今回我々は再手術症例を対象として前向き検討を行い，内視鏡下鼻内副鼻腔手術の前後に自覚症状およびQOLについてアンケート調査を行った。その結果，好酸球性副鼻腔炎患者群と非好酸球性副鼻腔炎患者群において，術前後の自覚症状やQOL障害度については一部を除き有意差はなく，ともに術後に改善していた。的確な手術と術後治療を行えば，一般的に難治性といわれる好酸球性副鼻腔炎といえども，再手術を行うことによって自覚症状やQOLの良好なコントロールを得ることができることが示唆された。

キーワード：好酸球性副鼻腔炎，再手術，自覚症状，内視鏡下鼻内副鼻腔手術

はじめに

慢性副鼻腔炎は，粘膿性鼻漏，鼻閉，嗅覚障害，頭重感などの生活に支障をきたす症状が長期にわたって持続し，かつ比較的罹患率の高い疾患である。近年，慢性副鼻腔炎はマクロライド系抗菌薬の少量長期投与などの治療法により治癒率の向上を得たものの，従来の治療法では改善しない予後不良例が徐々に増加してきており問題となっている。このような治癒寛解が困難な病態をもつ慢性副鼻腔炎患者の多くには鼻腔ポリープが認められ，手術を行っても再発を繰り返すことが多い。この難治症例の臨床的な背景を検討したところ，アスピリン喘息を含めた非アトピー性気管支喘息を合併している症例が多く，末梢血中の好酸球増多や鼻粘膜，鼻腔ポリープに著しい好酸球浸潤があることがわかってきた。現在そのような病態は好酸球性副鼻腔炎と呼ばれている[1]。好酸球性副鼻腔炎は，前述したように再手術を行っても予後が悪いことが予想されるため，一般的には術後の自覚症状の改善度が低いと考えられているが，再手術症例の術後成績に関する論文自体が少ないため未だ不明な点が多い。しかし，喘息を合併する副鼻腔炎と合併しない副鼻腔炎の再手術症例において自覚症状の改善度では有意差がなかったという報告[2]もあり，改めて検討が必要と思われる。

そこで我々は，慢性副鼻腔炎に対して内視鏡下鼻内副鼻腔手術を行った患者のうち再手術症例について術後の自覚症状，QOLについてアンケート調査による前向き検討を行い，好酸球性副鼻腔炎と非好酸球性副鼻腔炎について比較検討したので報告する。

対　象

2007年4月より2008年3月までの1年間に，東京慈恵会医科大学附属病院耳鼻咽喉科において，慢性副鼻腔炎の診断で内視鏡下鼻内副鼻腔手術を受けた患者のうち，過去に副鼻腔手術の既往があり，アンケート調査結果を術後6～18ヵ月まで回収できた患者118例を対象とした。対象の内訳は表1に示す。

方　法

慢性副鼻腔炎患者に対し，手術は罹患洞に対して

東京慈恵会医科大学耳鼻咽喉科学教室

表1　対象とした患者背景

	好酸球性副鼻腔炎	非好酸球性副鼻腔炎	*P value*
症例数	47	71	
性別（男/女）	37/10	48/23	0.19
年齢	53.6±13.0	53.4±14.3	0.79
術前CTスコア（Lund-Mackay）	15.6±5.8	10.3±6.4	<0.001
アレルギー性鼻炎（%）	44.7	38.0	0.48
気管支喘息（%）	44.7	19.7	<0.001
アスピリン喘息（%）	6.4	0.0	0.01
総IgE	293.1±514.4	174.4±275.7	0.06
末梢血好酸球数（%）	8.9±5.0	3.0±2.1	<0.001

内視鏡下鼻内副鼻腔手術を行い，必要に応じて鼻中隔矯正術もあわせて行った。また手術後に，生理食塩水による鼻洗浄および1〜2ヵ月間のクラリスロマイシン（クラリス®）やロキシスロマイシン（ルリッド®）によるマクロライド療法を行い，同時にベタメタゾン/d-クロルフェニラミン（セレスタミン®）やカルボシステイン（ムコダイン®）を併用し，必要に応じて鼻噴霧用ステロイドも使用した。気管支喘息合併例にはモンテルカスト（キプレス®）やプランルカスト（オノン®）も投与した。手術前，術後1〜3ヵ月（術後早期）と術後6〜18ヵ月（術後晩期）の時点で症状アンケート調査を実施した。アンケート項目は，2006年のJournal of Allergy and Clinical Immunology（JACI）で推奨されている副鼻腔炎に対する自覚症状スコア表を参考にして，12項目の自覚症状（鼻閉，鼻漏，後鼻漏，頬部痛，頭痛，倦怠感，嗅覚低下，耳閉感，咳，口臭，歯の痛み，発熱）と4項目のQuality of Life（QOL）に関する質問（勉強・仕事・家事への支障，日常生活への支障，思考力の低下，睡眠障害）について行い，各項目に関して0〜6までの7段階で評価してもらった[4]（図1）。

好酸球性副鼻腔炎に関しては，未だ明確な診断基準がないため，今回我々は両側性の慢性副鼻腔炎のうち，血中好酸球数400個/μl以上，もしくは副鼻腔粘膜（ポリープを含む）の組織中好酸球数について2視野の平均値として120個/視野（400倍）以上の条件を満たすものを好酸球性副鼻腔炎とした。その基準に満たないものは非好酸球性副鼻腔炎とし，今回の検討においてアレルギー性真菌性副鼻腔炎は除外した。

統計学的解析は分散分析（ANOVA）を行い，$p<0.05$を有意差ありと判断した。

結　果

術前の患者背景については，術前CTスコア（Lund-Mackay），気管支喘息（%），アスピリン喘息（%），末梢血好酸球数（%）の項目において，有意に好酸球性副鼻腔炎患者群で高値を示し，客観的な評価ではより重症度が高かった（表1）。しかし，自覚症状およびQOLに対するアンケート結果について検討したところ，術前のスコアにおいて好酸球性副鼻腔炎患者群と非好酸球性副鼻腔炎患者群間に有意差はなく，また両疾患群ともに術前と比較して術後（早期，晩期ともに）においてこれらのスコアが改善していた。

また，鼻閉，鼻漏，後鼻漏，頬部痛，倦怠感，嗅覚低下，耳閉感，歯の痛み，発熱，口臭に関しては，術前，術後早期，術後晩期いずれの時期においても，両疾患群の自覚症状スコアの有意差は認められなかった。しかし，術後早期の頭痛は非好酸球性副鼻腔炎患者群において有意に自覚症状スコアが高く，術後晩期の咳は好酸球性副鼻腔炎患者群において有意に自覚症状スコアが高かった（図2）。

QOLに対する質問では，勉強・仕事・家事への支障，日常生活への支障，思考力の低下，睡眠障害のすべての項目で，術前，術後早期，術後晩期いずれの時期においても，両疾患群のQOLスコアの有意差は認められなかった（図3）。

すべての項目の総計であるTotal Nasal Symptom

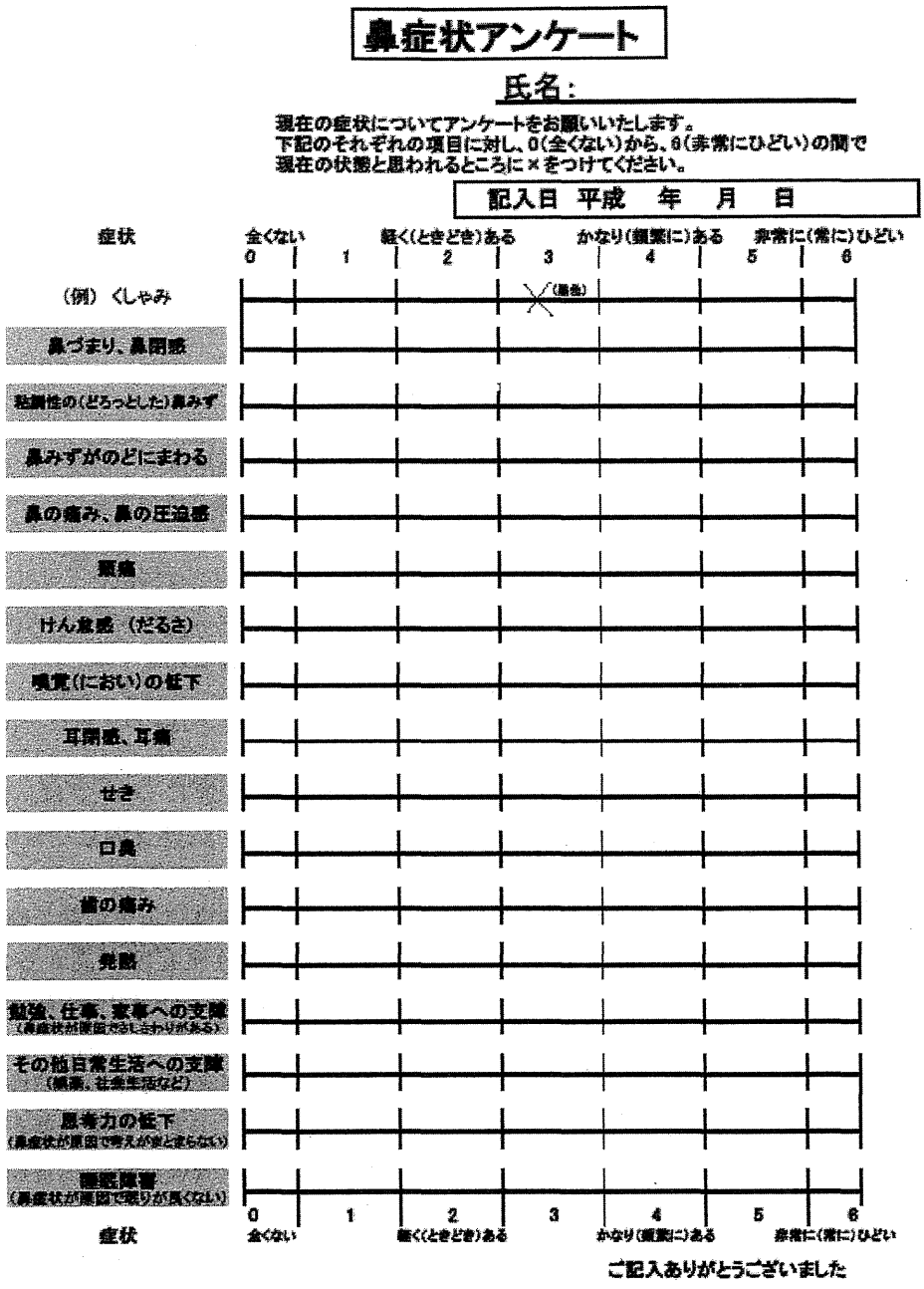

図1　鼻症状アンケート表

Score（TNSS）でも，術前，術後早期，術後晩期のいずれの時期においても，両疾患群の自覚症状スコアの有意差は認められなかった（図4）。

考　察

副鼻腔炎の手術後の再燃については，大きく分けて医療側の原因と患者側の原因とがある。医療側の原因としては，初回手術時の篩骨蜂巣の隔壁の残存や各副鼻腔の不十分な開放（Isthmus Surgery）による換気や排泄の障害と，不適切な術後治療が考えられている[5]。また，患者側の原因としては，今回対象とした好酸球性副鼻腔炎のような炎症局所あるいは全身的な問題によって再燃を繰り返す病態や，何らかの原因で線毛機能や免疫機能が低下している易感染性の病態などが挙げられる。

医療側の原因は我々の努力で解決することが可能と思われるが，患者側の原因は取り除くことが困難である。そのため副鼻腔炎の再燃を繰り返し再手術に至るような患者においては，特にその傾向が顕著になると予想され，一般的に非好酸球性副鼻腔炎患

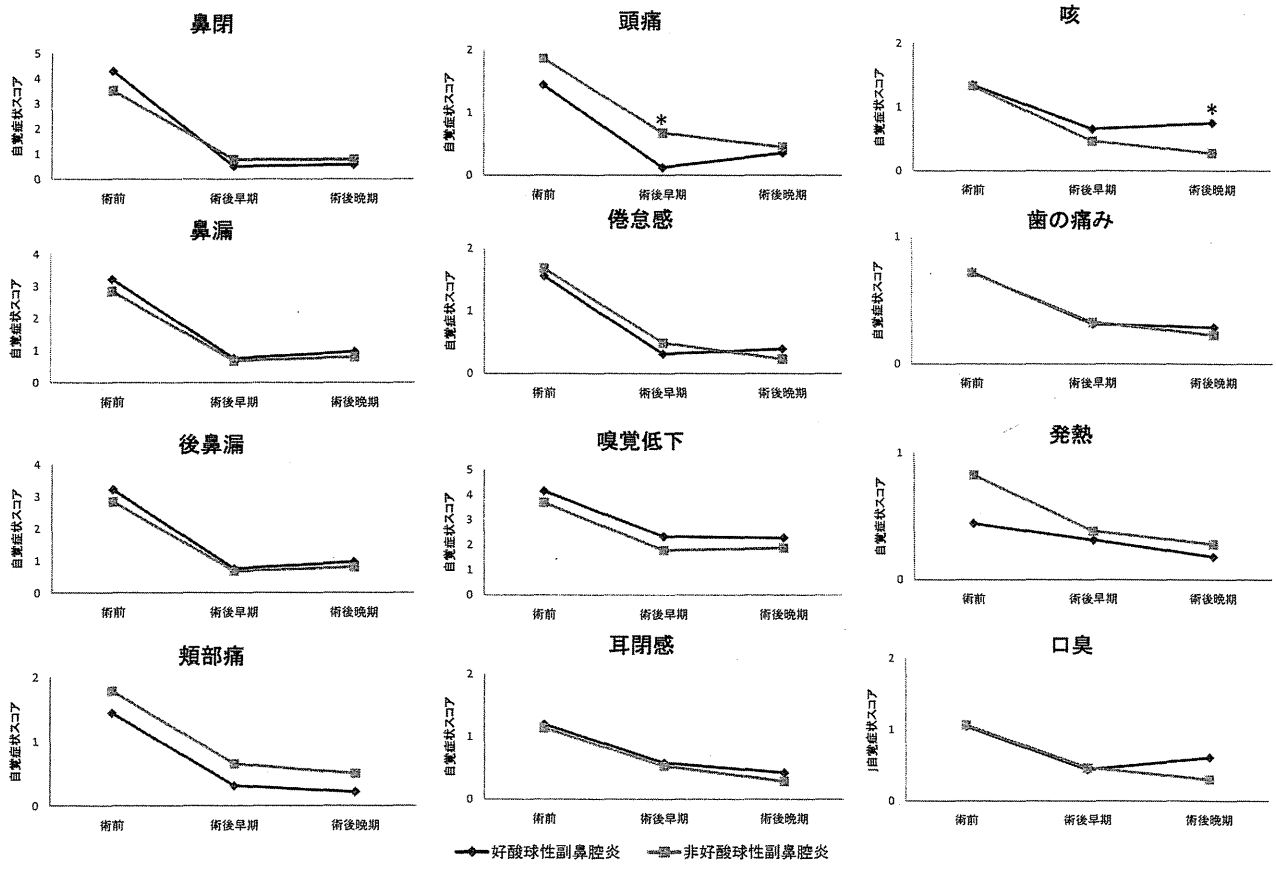

図2　自覚症状についてのアンケート結果

鼻閉，鼻漏，後鼻漏，頬部痛，倦怠感，嗅覚低下，耳閉感，歯の痛み，発熱，口臭に関しては，両疾患群の自覚症状スコアの有意差は認められなかった。しかし，術後早期の頭痛は非好酸球性副鼻腔炎において有意に自覚症状スコアが高く，術後晩期の咳は好酸球性副鼻腔炎において有意に自覚症状スコアが高かった。＊：$p<0.05$

者と比較して好酸球性副鼻腔炎患者のほうが自覚症状の改善度が低いと考えられている。

ところが，再手術症例のみを対象とした今回の検討の結果では，好酸球性副鼻腔炎患者群と非好酸球性副鼻腔炎患者群において，術前後の自覚症状やQOL障害度については一部を除き有意差はなく，ともに術後経過において改善していた。頭痛と咳において一部有意差を認めたことについては次のような要因が考えられる。まず，頭痛に関しては術前から非好酸球性副鼻腔炎患者群において自覚症状スコアが高い傾向があることから考えて，非好酸球性副鼻腔炎患者群では再手術に至る原因として医療側の要因が強く，初回手術の不十分な処置により生じた換気障害による頭痛である可能性が示唆される。一方，咳に関しては術後晩期にのみ好酸球性副鼻腔炎患者群で自覚症状スコアが有意に高いことから，術後晩期に至り副鼻腔炎の病態が改善しても，気管支喘息合併例がもともと有意に多いため，それによる症状の可能性がある。

このように自覚症状およびQOLスコアにおいて，術後急性増悪を繰り返す難治性の病態である好酸球性副鼻腔炎でも，非好酸球性副鼻腔炎に劣らない改善度が得られた要因としては，的確な手術手技と術後治療が考えられる。そもそも鼻内手術の概念は，各副鼻腔を単洞化し，鼻中隔彎曲に伴う鼻甲介の変位による形態異常を是正することで，各副鼻腔の換気や排泄を促し，副鼻腔粘膜を正常化することにある[6,7]。この概念は近年の好酸球性副鼻腔炎に対しても有効であり，鼻副鼻腔における細菌などの微生物や好酸球から産生されたサイトカインやロイコトリエンなどの炎症の悪循環因子の洗浄効率を上げ，鼻噴霧用ステロイドの副鼻腔粘膜への到達度を上げることにより術後の局所治療を容易にする効果がある[8,9]。また，術後管理の重要性は古くから言

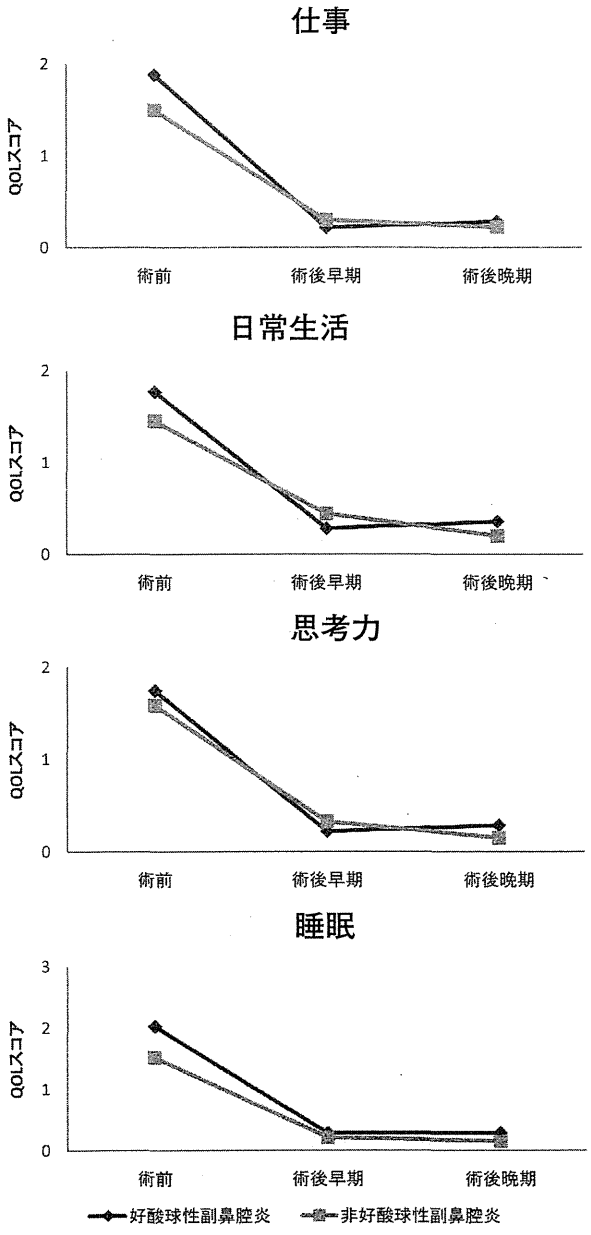

図3　QOLについてのアンケート結果
QOLに対する質問では，すべての項目で，術前，術後早期，術後晩期のいずれの時期においても，好酸球性副鼻腔炎と非好酸球性副鼻腔炎のQOLスコアの有意差は認められなかった。

われている[10]が，特に再手術後の術後治療は初回手術以上に重要である。我々の施設では生理食塩水による鼻洗浄および1～2ヵ月間の14員環マクロライド系抗菌薬によるマクロライド療法を行い，好酸球性副鼻腔炎に対しては同時に経口ステロイドを併用している。好酸球性副鼻腔炎に対しては術前のマクロライド療法の効果は比較的乏しいが，非好酸球性副鼻腔炎と同様に術直後の機械的損傷の加わった粘

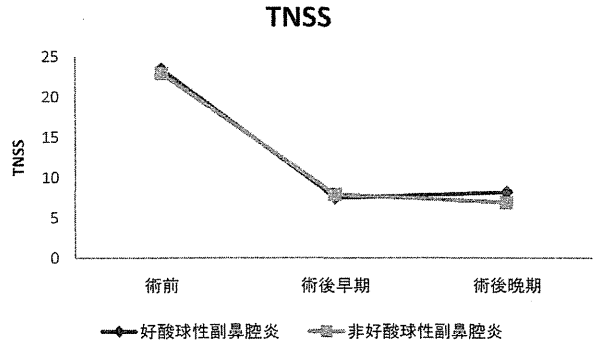

図4　Total Nasal Symptom Score（TNSS）
すべての自覚症状の総計であるTotal Nasal Symptom Score（TNSS）でも，好酸球性副鼻腔炎と非好酸球性副鼻腔炎の間に有意差は認められなかった。

膜の治癒過程において，抗炎症効果や過剰分泌の抑制効果は有効である[11]。その後は，生理食塩水による鼻洗浄と鼻噴霧用ステロイドを指示し炎症病態の増悪を予防する。また，気管支喘息合併例では，鼻茸中のシスティニルロイコトリエンなどの脂質メディエーター濃度が高値を示すという報告[12]もあり，抗ロイコトリエン薬や抗プロスタグランジンD_2・トロンボキサンA_2薬を併用している。それでも，感冒などの急性感染を契機に増悪することもあるので，適切な抗菌薬[13]とともに経口ステロイドを投与し病態を沈静化させるようにしている。

今回の我々の検討結果から，的確な手術と術後治療を行えば，一般的に難治性といわれる好酸球性副鼻腔炎といえども再手術を行うことによって自覚症状やQOLの良好なコントロールを得られることが示唆された。したがって，再手術に至るような難治性の症例においても，手術をためらうべきではないと考えた。

ま と め

慢性副鼻腔炎の再手術症例を対象として前向き検討を行った。内視鏡下鼻内副鼻腔手術の前後に自覚症状およびQOLについてアンケート調査を行ったところ，好酸球性副鼻腔炎患者群と非好酸球性副鼻腔炎患者群において，術前後の自覚症状やQOL障害度については一部を除き有意差はなく，ともに術後経過において改善していた。

これらの結果より，再手術に至るような難治性の症例，特に術後急性増悪を繰り返す好酸球性副鼻腔炎のような病態においても，的確な手術と術後治療

を行えば，患者の自覚症状やQOLの改善が再手術により期待できると考えた。

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Summary

Evaluation of Subjective Symptoms after Revision Endoscopic Sinus Surgery for Eosinophilic Chronic Rhinosinusitis

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Chronic rhinosinusitis often recurs after endoscopic sinus surgery (ESS). Recently, a recalcitrant pathophysiology, namely, eosinophilic chronic rhinosinusitis (ECRS), was recognized as one of the risk factors. Therefore, we conducted a prospective study of cases of revision surgery, conducted questionnaire surveys to assess the subjective symptoms and evaluate the quality of life (QOL) before and after ESS. The results revealed no significant differences in the subjective symptoms or QOL scores either before or after the surgery between ECRS patients and non-ECRS patients ; both groups improved after surgery. It is suggested that we can obtain good control of the subjective symptoms and QOL by revision surgery by selecting the precise operative method and postoperative treatment procedures.

Key words：eosinophilic chronic rhinosinusitis, revision surgery, subjective symptom, endoscopic sinus surgery

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