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Prognostic factors for recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps

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ABSTRACT

Objective: In this study, we aimed to clarify the prognostic factors affecting the ethmoid condition during a long-term follow-up after endoscopic sinus surgery in patients with chronic rhinosinusitis with nasal polyps (CRSwNP).

Methods: Thirty-six patients with CRSwNP underwent surgery from December 2008 to February 2012. All surgeries were performed by one surgeon, and all patients were followed up for at least 2 years postoperatively. We investigated the association of postoperative endoscopic findings with clinical parameters, mucosal eosinophil count and mRNA expression of CCL11, IL-5, and IFN-gamma in nasal polyps.

Results: Seventeen patients (47.2%) had severe mucosal edema, and the patency of each sinus was not confirmed during the >2-year follow-up. The mucosal eosinophil count and two eosinophil-associated factors, namely the CCL11 and IL-5 mRNA levels, were higher in the severe mucosal edema group than in the control group. The severe mucosal edema group was divided into two subgroups: the steroid-responsive and -resistant groups. Five patients (13.9%) had frank polyp formation because the oral steroids were less effective. The mucosal eosinophil count was significantly different among the four groups, including the control group ($p = 0.001$); however, the CCL11, IL-5, and IFN-gamma mRNA levels were not significantly different. Although the IL-5 mRNA level was not significantly different among the four groups, it tended to increase when the sinus condition worsened. In the severe mucosal edema group, a higher IL-5 mRNA level was associated with earlier severe mucosal edema in the ethmoid cavity.

Conclusion: The IL-5 mRNA level is associated with the time of severe edema formation in the ethmoid cavity. This finding permits early intervention on the postoperative course and would prevent polyp recurrence.

1. Introduction

Chronic rhinosinusitis (CRS) is a heterogeneous disease, and its pathogenesis is still uncertain. CRS is defined as inflammation of the nose and paranasal sinuses characterized by typical symptoms, endoscopic findings, and computed tomography (CT) characteristics that last for at least 3 months according to the European Position Paper on Rhinosinusitis and

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Nasal Polyps (EPOS) [1]. Endoscopic sinus surgery is the gold standard procedure for patients with CRS that is unresponsive to maximum medical treatment. However, CRS characterized by mucosal eosinophilia, asthma, residual ethmoid cells, and higher CT and polyp scores has a tendency to recur after the surgery [2–9].

We proposed eosinophilic chronic rhinosinusitis (ECRS) as a classification in 2001[10], because in Japan, mucosal eosinophilia is a more important prognostic factor for the surgical outcome than is the presence of nasal polyps [3,10]. In Western countries, CRS is divided into CRS with nasal polyps (CRSwNP) and CRS without polyps (CRSsNP) [1]. The clinical features of ECRS in Japan are nearly the same as those of CRSwNP in Western countries [3,11,12]. The mucosal eosinophil count was recently reported to be a significant prognostic factor in countries other than Japan, and the term ECRS has also been used outside of Japan [7,13]. The understanding of CRS phenotypes has gradually increased [14], but the immunologic factors affecting postoperative recurrence remain to be clarified. In this study, we investigated prognostic factors, including cytokine patterns, for recurrence after endoscopic sinus surgery in patients with CRSwNP during a long follow-up period.

2. Methods

2.1. Patients

We prospectively collected and retrospectively analyzed the data of this study. Thirty-six patients with bilateral nasal polyps underwent endoscopic sinus surgery due to failed medical management from December 2008 to February 2012. The diagnosis of CRS was based on the EPOS criteria [1]. This study excluded patients treated with oral steroids or antimicrobial agents within 4 weeks before the surgery as well as patients with unilateral disease, fungal disease, antrochoanal polyps, allergic fungal rhinosinusitis, and cysts of the paranasal sinus. Demographic and clinical characteristics obtained from the patients prior to the surgery included sex, age, history of sinus surgery, asthma, and aspirin-exacerbated respiratory disease. Eosinophilic otitis media was diagnosed by previously established criteria [15]. Perennial allergic rhinitis was diagnosed based on the total IgE concentration and a fluorescence enzyme immunoassay for house dust mites and *Dermatophagoides pteronyssinus*. Five symptoms were assessed: nasal obstruction, anterior nasal discharge, posterior nasal discharge, facial pain, and decreased sense of smell. The severity of each symptom was evaluated according to a 5-point (score of 0–4) Likert scale. Aspirin-exacerbated respiratory disease and asthma were diagnosed by a pulmonologist. The diagnosis of hypersensitivity to aspirin was based on a reported history of adverse reactions associated with aspirin and/or other nonsteroidal anti-inflammatory drugs. The preoperative polyp-grading system utilized a 5-point scale (score of 0–4) according to recommended guidelines [16]. Preoperative computed tomography scans were scored according to the classification described by Lund and Mackay [17]. The T&T Olfactometer Test Kit (Takasago Industry, Tokyo, Japan) is a standard olfactory test in Japan that includes five odorants [β-phenylethyl alcohol (A, smells like a rose), methyl cyclopentenolone (B, smells like burning), isovaleric acid (C, smells like sweat), γ-undecalactone (D, smells like fruit), and skatole (E, smells like excrement)]. These odorants have eight concentrations ranging from −2 to 5, except for odorant B, which ranges from −2 to 4. The detection threshold was defined as the lowest concentration detectable by the patient, whereas the recognition threshold was defined as the lowest concentration at which the odor can be identified. The detection and recognition thresholds of the five odorants were averaged to evaluate the olfactory acuity. We counted mucosal eosinophils under three high-power fields (×400) containing the densest cellular infiltrate beneath the epithelial surface, and the mean number of eosinophils was calculated. We defined ECRS according to the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) study criteria [18]. The control group comprised five patients with pituitary tumors (3 males and 2 females, mean age of 70.4 years).

2.2. Treatment and postoperative evaluation

All patients underwent surgery by one surgeon (S-I H) to avoid bias in surgical skill. He performed a complete ethmoidectomy and widely communicated with each of the three sinuses. All patients were followed for at least 2 years after the surgery. Medical therapy after surgery included 2 tablets of Celestamine® (which contained 0.25 mg betamethasone and 2 mg d-chlorpheniramine per tablet) for 2 weeks and macrolide antibiotics for 2–3 months. A topical nasal spray was administered once or twice a day, and saline irrigation was performed twice a day.

Postoperative endoscopic findings were evaluated on a 0- to 3-point scale based on the modified Lund–Kennedy mucosal edema score [19]: 0, no visible mucosal edema and confirmation of the capillary vessels under the mucosa; (1) mild mucosal edema without obliteration of the ethmoid cavity and confirmation of the patency of each sinus; (2) severe mucosal edema obliterating most of the ethmoid cavity and lack of confirmation of the patency of each sinus; and (3) frank polyposis. Patients with a score of ≥2 were assigned to the severe mucosal edema group (recurrence group) in this study. We administered 2 tablets of Celestamine® with or without antimicrobial agents to the patients with a score of ≥2 for a week. If the effect was insufficient, the patients could take them up to a maximum of 2 weeks. When the patients had a score of ≥2 again, we repeated it. All the patients with asthma did not have oral steroids for controlling asthma. Within the severe mucosal edema group, we assigned patients to the steroid-resistant group when the endoscopic score was 3 and frank polyposis was present in spite of taking oral steroids. The other patients were assigned to the steroid-effective group.

2.3. Sampling and total RNA extraction

During the surgery, we removed nasal polyps from patients with CRSwNP and the uncinate process from patients with pituitary tumors as a control. The tissues were immediately

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