Predictive outcomes of functional endoscopic sinus surgery in patients with chronic rhinosinusitis

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Objective
This article aims at addressing some inflammatory markers obtained from patients who underwent a functional endoscopic sinus surgery for refractory chronic rhinosinusitis (CRS) to predict the outcome of such surgeries according to the inflammatory load and to determine whether certain immune markers can predict a poor prognosis in these patients.

Methods
Fourteen patients (eight women and six men) with diffuse rhinosinusitis as evident from a computed tomography scan but without nasal polyposis underwent ethmoidectomy. All patients had undergone biopsies of the ethmoid sinuses at the time of surgery. All tissue samples were subjected to immunohistochemical staining using CD3, CD4, CD8, and interleukin (IL)-5 antibodies, and the number of lymphocyte subsets (CD3, CD4, and CD8) and IL-5-expressing cells at the time of surgery were compared with the clinical response and nasal endoscopic findings 6 months after surgery.

Results
Only six patients showed an improvement with a decrease in nasal symptoms and a decrease in the need for medications. Eight patients had an unchanged status or worsened, with disabling rhinorrhea and repeated sinusitis.

Conclusion
Almost more than half of the patients with CRS and a diffuse mucosal disease do not respond to surgery. T lymphocytes play an important role in the pathophysiology of CRS. An increased number of IL-5-expressing cells in the ethmoid sinuses at the time of surgery could predict a poor prognosis. It may eventually be possible to classify patients with CRS into different groups with different prognoses.

Keywords:
chronic rhinosinusitis, functional endoscopic sinus surgery, immune markers

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Introduction

Chronic rhinosinusitis (CRS) is a common clinical syndrome characterized by inflammation of the mucosa of the nose and the paranasal sinuses [1]. This disorder is typically classified into CRS with nasal polyps and CRS without nasal polyps. The etiology and pathogenesis of CRS is a subject of intense debate, but bacteria, viruses, and fungi have all been implicated in the establishment of the inflammatory process [2]. Abnormalities in host response to these common agents, including defective cytokine and chemokine signaling of the nasal mucosa, have been suggested to underline the persistence of the inflammatory state [3].

Through recent advances in research, our understanding of CRS has evolved to consider it an inflammatory condition of the mucosa induced by multiple factors. These concepts fail to provide a sufficient explanation for the presence of a subset of patients with refractory CRS who failed to respond to conventional functional endoscopic sinus surgery (FESS). The grade of inflammation is the most important predictor of long-term outcomes [4]. Among numerous studies in the literature on the prognostic factors that might determine outcome in FESS, very few have dealt with the assessment of their predictive potential in terms of outcome, and none have attempted to determine the extent of such a prediction [5]. Numerous studies have shown that the degree of sinonasal inflammation as measured by computed tomography (CT) scan or endoscopy fails to correlate with the extent of symptoms experienced by the individual patient [6]. A patient may therefore have debilitating symptoms with only mucosal thickening or vice versa. The lack of agreement between an objective assessment and patient-centered assessment is not unique to CRS, but can also be found in conditions such as obstructive sleep apnea and asthma [7]. FESS is most typically reserved for patients who are refractory to standard medical treatments. The preponderance of quality-of-life studies has shown that these patients will experience a statistically and clinically significant improvement after FESS, but will likely still be left with some measurable burden of disease [8].

Long-term results of FESS have shown that in almost 50% of the cases, there is persistence of some of the

preoperative abnormalities or significant residual disease [9]. The patients with the most extensive involvement of the sinuses also have concomitant atopy and asthma [10]. The presence of allergy may be a risk factor for the development of CRS [11]. This hypothesis has been predicted on the findings of positive skin tests in 57% of patients operated for CRS [12]. When the pathologic features of CRS are assessed, a different inflammatory response can be found in the sinuses of allergic and nonallergic patients with this disease [13]. Allergic patients with CRS have an increase in tissue eosinophils, mast cells, and lymphocytes [14]. The aim of this study is to evaluate the prognosis of FESS in patients with CRS and to assess whether an indicator of immune response in the biopsy specimens obtained at the time of surgery can predict a poor response to surgery in these patients.

Patients and methods

Fourteen patients, eight women and six men, with symptoms of CRS on coronal CT scan but without nasal polyposis were included in this study. The mean age of the patients was 30 years. The patients had chronic sinusitis in the form of nasal obstruction, rhinorrhea, and headache lasting more than 3 months and resistant to medical treatment that included antibiotics, antihistaminics, and corticosteroids. FESS was performed for all patients under general anesthesia in October-6 University Hospital's Otorhinolaryngology Department between October 2011 and September 2012. The operative procedure included middle meatal antrostomy with exposure of the inflamed ethmoidal cells. Biopsy specimens were obtained from ethmoid sinuses. Two tissue samples were obtained from each patient so that each of the 28 samples was subjected to immunohistochemical staining using CD3, CD4, CD8, and interleukin (IL)-5 antibodies to assess the number of total T cells, T-helper lymphocytes, suppressor/cytotoxic lymphocytes, and IL-5-expressing cells, respectively. The paraffin-embedded tissue sections were deparaffinized in xylene and rehydrated through absolute alcohol. Antigen retrieval in citrate buffer (pH 9, Lab Vision Cat# AP9003) was used after the sections were treated in a microwave at 8 W for 5–6 min and then at 3 W for 10 min; the sections were then left to cool for 20 min. Peroxidase and protein block were performed. Then, the slides were incubated overnight with each of the primary antibodies at room temperature using CD3 antibody (rabbit polyclonal antibody 7 ml, Cat# 103A-78), CD4 (rabbit monoclonal antibody 7 ml, Cat# 104R-18), CD8 (mouse monoclonal antibody 7 ml, Cat# 108M-98), and IL-5 (rabbit polyclonal antibody dilution 1 : 250) from Cell Marquee (California, USA) followed by rinsing in PBS (pH 7.6). This was followed by the secondary biotin-conjugated antibody for 1 h and finally the peroxidase-conjugated streptavidin for another hour. Diaminbenzidine tetrachloride (freshly prepared) was added for 25 min, and then counterstained in Harris hematoxylin, followed by dehydration, clearing, and mounting.

Quantification of the cellular infiltrate

The cellular infiltrate including the CD3-positive, CD4-positive, CD8-positive, and IL-5-positive cells were immunohistochemically quantified. Slides were counted in a blinded manner using a light microscope. Two slides per measure were assessed, from which 3–4 fields were counted and the results were expressed as positive cells per high-power field [15]. The fields were chosen with maximal density of inflammation.

Assessment of preoperative and postoperative symptoms was performed by a chronic sinusitis score (visual analog score) that focused on three major symptoms: headache, nasal obstruction, and rhinorrhea. These were assessed subjectively by the patient on a scale from 0 to 10 according to severity, where 0 indicated that no symptoms were present and 10 indicated the most severe symptoms. Postoperative endoscopic evaluation was performed after 2 months and at the last visit (6 months) for objective evaluation of the nose.

Statistical analysis

Statistical analysis was carried out using the SPSS program version 16 [16].

Data are presented as Mean ± SEM. The Student *t*-test and analysis of variance, followed by Bonferroni's post-hoc analysis were used for comparisons between groups. The level of statistical significance was set at *P* value of less than 0.05.

Results

Six of fourteen patients improved (responders), whereas eight patients had an unchanged status or even worsened after surgery (nonresponders). However, after surgery, the two groups that were formed (responders and nonresponders) were significantly different in terms of all symptoms. The clinical symptoms score categorized all patients into the same group (Table 1).

Pathologic assessment and response to surgery

Immunohistochemical staining was performed to assess the amount of inflammatory cells (CD3-expressing, CD4-expressing, CD8-expressing, and IL-5-expressing cells) present at the time of surgery in the mucosa of the ethmoid sinuses. The results were compared with the clinical evaluations obtained 6 months after surgery.

There was a statistically significant difference between the responder and the nonresponder groups in the number of each of CD3-positive, CD4-positive, and CD8-positive cells, as the mean values of CD3-positive, CD4-positive, and CD8-positive cells were significantly higher in the nonresponder than in the responder group ($P<0.05$) (Table 2, Figs 1–5). There was an increase in the mean value of the IL-5 cell population in the nonresponder group compared with the responder group, with a statistically significant difference ($P<0.05$) (Table 2, Figs 6 and 7).

Table 1 The results of clinical symptoms are presented as median for the six responders and eight nonresponders at the 6-month follow-up

	Chronic sinusitis score (0–10)			
	Headache	Obstruction	Rhinorrhea	Total
Preoperative assessment				
Nonresponders	6	8	8	8
Responders	7	8	8	
Statistical significance (*P*)[a]	0.71	0.7	0.46	0.9
Postoperative assessment				
Nonresponders	4	8	8	8
Responders	1	1	2	2
Statistical significance (*P*)[a]	<0.001	0.001	0.001	<0.002

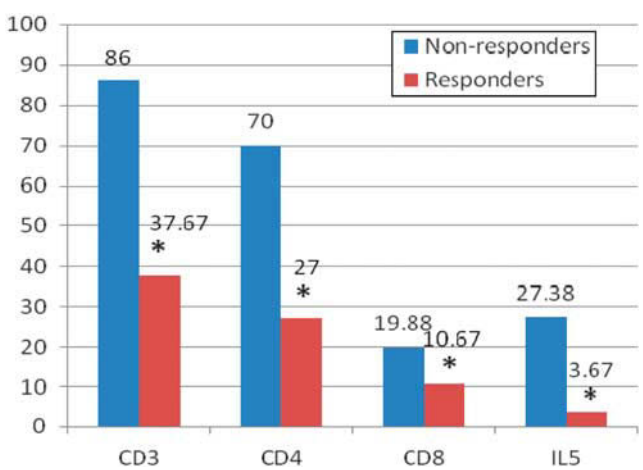
[a]Significant decrease compared with the nonresponder group ($P<0.05$).

Table 2 Comparison between the two groups (responders and nonresponders) in the mean values of CD3-positive, CD4-positive, CD8-positive, and interleukin-5-positive cells

	Group	Number	Mean	SD	SEM
CD3	Responders	6	37.6667[a]	7.42069	3.02948
	Nonresponders	8	86.0000	6.92820	2.44949
CD4	Responders	6	27.0000[a]	7.23878	2.95522
	Nonresponders	8	70.0000	14.57983	5.15475
CD8	Responders	6	10.6667[a]	2.50333	1.02198
	Nonresponders	8	19.8750	3.13676	1.10901
IL-5	Responders	6	3.6667[a]	0.81650	0.33333
	Nonresponders	8	27.3750	5.92663	2.09538

IL, interleukin.

Figure 1

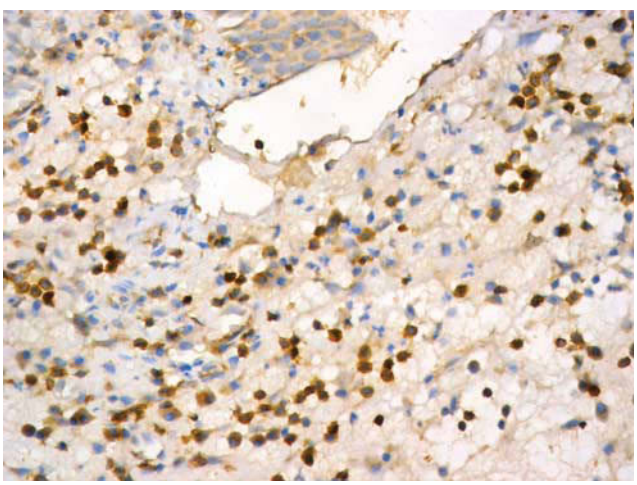


Comparison between the two groups (responders and nonresponders) in the mean values of CD3-positive, CD4-positive, CD8-positive, and interleukin (IL)-5-positive cells. *Significant decrease compared with the nonresponder group ($P<0.05$).

Discussion

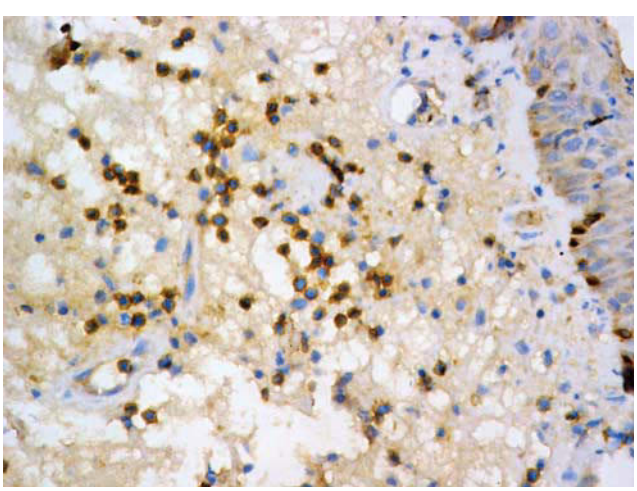
Although FESS is the current gold standard, the extent of surgery used remains highly variable and is not evidence based. Many reports suggest that the inflammatory load is the most important predictor of long-term outcome. Patients with a high inflammatory load have a higher probability of being refractory to standard FESS [4]. Chronic sinusitis is treated by surgery when recurrent infection or the major symptoms of facial pain, nasal obstruction, and rhinorrhea do not improve with medical therapy [17].

Figure 2



Cytoplasmic immunohistochemical expression of CD3 in a nonresponder case (× 400).

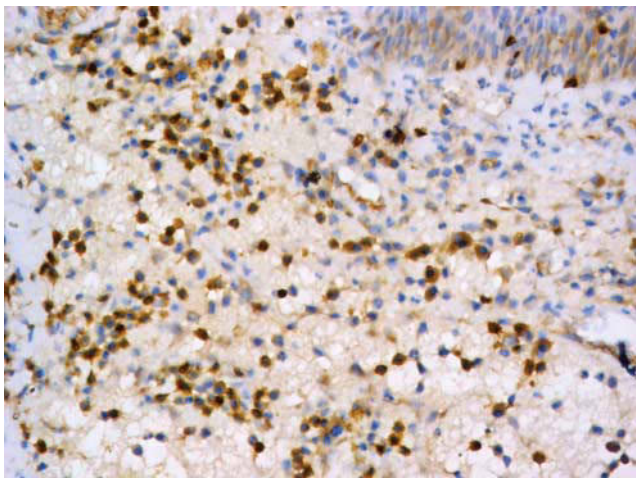
Figure 3



CD4 immunohistochemical expression in a responder case (× 400).

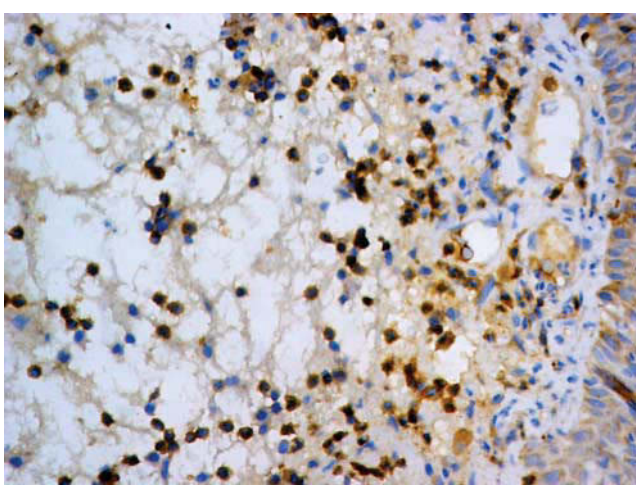
This study was carried out to establish the long-term prognosis after ethmoidectomy and middle meatal antrostomy in patients with CRS and to determine whether there were some characteristics of the inflammation

Figure 4



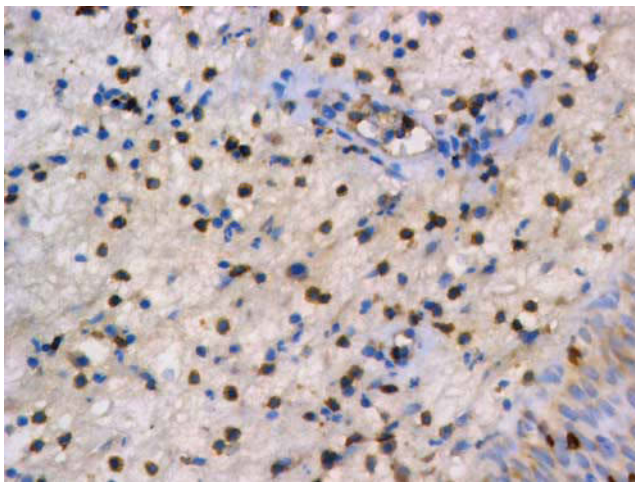
CD4 immunohistochemical expression in a nonresponder case (× 400).

Figure 5



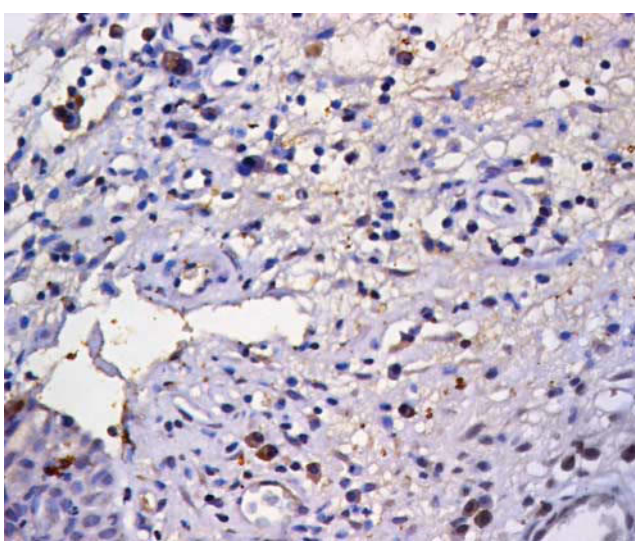
CD8 immunohistochemical expression in a nonresponder case (× 400).

Figure 6



Interleukin-5 immunohistochemical expression in a nonresponder case (× 400).

Figure 7



Cytoplasmic immunohistochemical expression of interleukin-5 in a responder case (× 400).

found in the sinus at the time of surgery that predict a poor prognosis. All patients had extensive bilateral mucosal disease on the CT scan of the sinuses but not nasal polyposis. Six months after surgery, more than half the patients did not shown any improvement. Endoscopic sinus surgery with ethmoidectomy and drainage of the natural ostia gives the best relief of headache and nasal obstruction but nasal discharge will often persist, and infections recur even when the meatotomy remains patent [18]. The reported percentage of overall subjective improvement after a surgical intervention for nonpolyposis patients with CRS is between 80 and 90% [19]. However, the percentage of patients who improved after surgery decreased to 50% when an objective assessment by sinus endoscopy was performed [9]. In this study, less than a 50% response to surgery was found when the patients were followed up for 6 months. Pain, nasal obstruction, and nasal discharge were equally disturbed in both groups before surgery, but nasal discharge and congestion persisted as main complaints in nonresponders and explain their persistent use of medications after surgery. Moreover, to assess whether a biologic marker could predict the absence of response to surgery, biopsy specimens were obtained from the most affected regions of the ethmoid sinuses at the time of surgery. The inflammatory cells measured were the lymphocyte subsets (CD3, CD4, CD8) and the number of cells expressing IL-5. These parameters were compared between responders and nonresponders.

T cells are the primary effectors of cell-mediated immunity, with subsets of T cells maturing into cytotoxic cells capable of lysis of virus-infected or foreign cells [20]. The CD4 T-helper cell is the inducer of all immunological

process, and its presence is indicative of an active immunologic process [21]. T-helper cells induce B-cell differentiation and cytotoxic T-cell proliferation, and produce various lymphokines.

In our study, we investigated the role of T lymphocytes in the pathophysiology of persistent inflammation in chronic sinusitis. CD3 total cells were observed more in ethmoid sinus mucosa of the nonresponder group than in responders, with a significant difference. When the highest concentration of T-cell subsets was investigated, CD4-positive cells were observed more than CD8-positive cells.

Ethmoid sinuses are reported to be exposed more extensively to the environment [22]. Exposure of the sinus mucosa to environmental irritants could lead to a predominance of CD4-positive cells in the ethmoid sinuses because these cells are important in the initiation and regulation of inflammation.

Studies on the inflammatory process and the factors affecting the inflammatory process in patients with chronic sinusitis can be found in the literature. In the study by Driscoll *et al*. [23], children with chronic sinusitis had a predominance of CD4-positive cells in the sinus mucosa compared with normal sphenoid tissue. There was no significant difference in the number of CD8-positive cells. CD4-positive and CD8-positive cells were more numerous in the apical portion of the submucosa (immediately beneath the epithelium) than in the basal portion in patients with chronic sinusitis and patients with normal sphenoid tissue. The authors concluded that the preponderance of inflammatory cells in the superficial portion of the submucosa, closest to the epithelium itself, may, in response to injurious stimuli, secrete chemotactic or growth factors that attract inflammatory cells to the surface.

In the study by Hamilos *et al*. [24], there were more CD4-positive cells than CD8-positive cells in the sinus mucosa, especially in allergic patients.

Kamil *et al*. [25] reported a significant increase in the CD4-positive to CD8-positive cells ratio in the ethmoid sinus mucosa compared with that in the maxillary sinus and inferior turbinate in allergic patients with CRS. The assessment of T lymphocytes subsets in this study showed a trend for more T cells in the ethmoid sinuses, with a clear predominance of CD4-helper cells.

In the literature reviewed above, it can be seen that the main T-cell subset in the chronic inflammation of the nose and paranasal sinuses is CD4 T-helper cells [25], which is also true for our study.

The predominance of CD8-positive cells has also been reported infrequently. Grevers *et al*. [26] examined frozen sections of inferior turbinates from 14 patients with chronic sinusitis. They found a significant increase in CD3, CD4, and CD8 T cells in the nasal mucosa. In the epithelial layer, the CD4 to CD8 ratio was 1 : 5. The authors concluded that accumulation of CD8-positive cells in the epithelium might indicate that selectivity of cellular infiltration is one of the immunological reasons for the persistent and chronic nature of inflammation in chronic sinusitis.

Nishimoto *et al*. [21] reported significantly more CD8-positive cells than CD4-positive cells in the submucosa of adults with chronic sinusitis. They concluded that CD4-positive cells predominate in normal immune environments, whereas abnormal environments, such as in chronic sinusitis, have a reversal of the cell types, with a preponderance of CD8-positive cells.

Lymphocytes affect the immune response through cell contact and the release of cytokines. Jyonouchi *et al*. [14] found an increased production of the T-helper type 2 cytokines IL-4 and IL-5 in the airways of patients with asthma and in the nasal and sinus mucosa of patients with allergy and CRS. CD4-positive T lymphocytes are the major source of IL-5 in allergic tissue, but mast cells and eosinophils also release IL-5. In this study, the number of cells expressing IL-5 in the ethmoid sinuses at the time of surgery was significantly increased in nonresponders. In a previous study, CD4-positive cells with a T-helper type 2 phenotype were increased in patients with CRS [27]. In the present study, it is not surprising to find that the changes in the ethmoidal sinus mucosa are a marker for prognosis in patients with CRS who do not respond to surgery. Previous studies have shown greater cytokine expression in the ethmoid sinus, which was the site with the most inflammation in CRS [25]. The present results also suggest that in patients with an increased inflammatory response related to IL-5 production, opening the sinus cavities would have a negative effect on the response to surgery. This effect might occur by exposing the sinuses to environmental allergens, infectious agents, and irritants and possibly by perpetuating the chronic inflammation that was present in the nasal cavity before surgery. The determination of IL-5-positive cells in the ethmoid sinuses may help determine whether surgery is indicated in patients with diffuse CRS. Because there is no surgical alternative for the time being, environmental control and immunotherapy is suggested in patients with the most cells expressing IL-5 in the ethmoid sinus to control their symptoms.

Conclusion

Approximately more than half of patients with CRS and diffuse mucosal disease do not respond to surgery. T cells play an important role in the pathophysiology of CRS. In these patients, CD4-positive T-helper cells are the main subtypes of T cells and are important for the initiation and regulation of inflammation. An increased number of cells expressing IL-5 in the ethmoid sinuses at the time of surgery could predict a poor prognosis. It may eventually be possible to classify patients with CRS into different groups with a different prognosis, which in turn may necessitate different therapeutic interventions. CRS is a more medical problem than a surgical case, except if

there is a pure surgical indication that cannot be corrected by treatment.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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