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Correlation between the cytology of the nasal middle meatus and BAL in chronic rhinosinusitis*

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SUMMARY

The relation between chronic rhinosinusitis (CRS) and the associated lower airways involvement is not clear yet. In this context, the aim of this prospective study was to evaluate the correlation between middle meatal lavage (MML) and bronchoalveolar lavage (BAL) cytology in adult CRS patients. Based on clinical history and pulmonary function changes, CRS patients were divided into three subgroups: asthma, small airway disease (SAD) and normal lower airway (NLA) subgroups.

Preoperatively, 50 MMLs and 25 BALs were performed in 25 CRS patients scheduled for FESS. At 1000X power microscopic magnifications, 48 MML and 24 BAL cytospin slides were examined for total and differential cell counts (DCC). This study showed that eosinophils were the dominant inflammatory cells in MMLs of the asthma subgroup and were significantly correlated to FEVI ($p=0.042$) and Tiffineau index ($p=0.037$). On the other hand, neutrophils were the dominant inflammatory cells in MMLs of the SAD subgroup and significantly correlated to FEF75% and Tiffinau index ($p=0.013$ and $p=0.012$ respectively). There was no significant correlation between MML and BAL cell differential counts in CRS patients ($p>0.05$). The data showed that the lower airways involvement in CRS patients could be related to the dominant type of inflammatory cells in the upper airways.

Key words: nasal cytology, BAL, sinusitis, asthma, small airway disease

INTRODUCTION

Since the time of Galen (130-200 AD), physicians have been aware of the coexistence of a syndrome including upper airways inflammatory disorders and associated lower airways involvement [1]. This has been interpreted in two opposing ways: either the upper airways disease and the asthma are different and separate entities, with the former pathology being a potential risk factor for the latter, or the upper airways disease and the asthma are an expression of the same disease, involving simultaneously upper and lower airways, probably because of a common aetiology [2].

Nasal secretions probably represent the first line of defence in which leukocytes play an important role [3,4]. It is also well known that secretions from most of the paranasal sinuses (the frontal, maxillary, and anterior ethmoidal complexes) drain into the middle meatus. Therefore, an inflammation of the sinus mucosa will quantitatively and qualitatively modify the leukocyte ratios in the mucus that drains towards the middle meatus. These inflammatory changes may influence the remaining lower respiratory system and induce or exacerbate related inflammatory changes in the lower airways. The bronchoalveolar lavage (BAL) is the window to the lungs. It provides direct and safe sampling that can be compared to endobronchial or transbronchial biopsies [5].

The aim of this work was to study the cytology of the middle meatus lavage (MML) in patients with CRS and compare it with the potential inflammatory changes found in the BAL of the same patients. Furthermore, these cellular changes were correlated with spirometric lower airways functional changes.

METHODS

Twenty-five adult CRS patients were enrolled in this prospective study. All patients were scheduled for functional endoscopic sinus surgery (FESS) after failure of medical treatment. The study population included 18 males and 7 females with ages ranging between 25-66 years and a mean age of 34.1 years. Chronic rhinosinusitis was diagnosed in these patients based on the definition of the consensus report of the rhinosinusitis task force group [6]. Patients with cystic fibrosis, primary ciliary dyskinesia, recognised immunodeficiency or other systemic

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diseases that can affect the upper and lower airways were excluded. In addition, no medications were allowed one month before the study except for asthma medications.
The study was approved by the Ethical Committee of the hospital (Academic Hospital, Free University Brussels), and all patients gave an informed consent. No control subjects were included, as we judged it was not ethical to perform BAL in completely normal persons.

Lower airways assessment
Subjective anamnesis of the lower airway symptoms including cough, sputum, dyspnea, chest pain, wheezes and haemoptysis was performed. The diagnosis of asthma and small airway disease was obtained according to the international guidelines for asthma diagnosis [7]. The diagnosis of asthma was based on the patient's medical history, physical examination, and objective measurements of pulmonary function.
Pulmonary function assessment
The assessment was performed according to the standardisation of lung function tests of the European Respiratory Society (1993) using SensorMedic's, pulmonary function equipment, U.S.A. FVC, FEV1, FEVI/FVC% and FEF75% were all calculated from the best flow-volume curves and reference values were obtained according to the European guidelines [8]. An obstructive ventilatory defect was defined as a decrease in FEV1 to any decrease in VC, i.e. a decrease in the FEV1/VC ratio or Tiffeneau index $<$ 70%. Small airway disease was also suspected if the Tiffeneau index was above 70% but with a concomitant decrease of FEF 75% fewer than 70% of the predicted value.
Asthma and small airway disease were diagnosed according to the international guidelines of asthma diagnosis [7].

Specimen collection
The specimens were collected in the operating room before the endoscopic sinus surgery was started.
- Bronchoalveolar lavage (BAL):

A sterilised flexible fibreoptic bronchoscope was passed into the airways through the endotracheal ventilation tube and gently impacted or wedged into a subsegmental bronchus (right middle lobe).
Sterile saline, buffered and warmed to body temperature was then injected into the subsegment through the bronchoscope biopsy channel and then aspirated.
A standardised 5x20 ml aliquot regimen was used, each aliquot being injected under minimal hand pressure over about 10 seconds with immediate aspiration with low aspiration suction pressure of 80cm H_2O. The large volume will preferentially sample the lung parenchyma with its inflammatory component [9]. The collected specimens were placed in special containers surrounded by ice and sent directly for cytological examination.

Middle meatal lavage (MML):
Before the surgery, nasal endoscopy was performed with a 30-degree wide angle, 4.00 mm rigid endoscope (Wolf, Tuttingen, Germany) attached to a video camera. Examination of both nasal cavities was performed, focusing on the middle meatus and site of discharge. An assessment of nasal polyposis (if present) was performed without decongestion according to Lund –McKay [10]. To avoid any effects of local anaesthetics and vasoconstrictors over cellular count and morphology, samples were obtained without these medications. In addition, with a view to avoid the diurnal variations described by Jankowski [3], the samples were obtained in the morning hours, between 9 and 12 a.m. A sterilised 2-way irrigation suction tip was used. It was connected on one side to a 20-ml syringe full of sterile buffered physiological saline at body temperature. On the other side, it was connected to a special double way bottle attached to the aspiration machine. The saline was injected under minimal hand pressure over 30 seconds into the middle meatus with the guidance of the nasal endoscope. This allowed for perfect sampling of mucus from the sinuses and its related mucous membrane. The bottles containing the collected MML were put in a container with ice and sent directly for cytological examination. The procedures were similar in both nasal passages.

Cytological examination
In this study using the cytospin method, middle meatal (MM) secretions and BALs were processed directly after their collection. The cellular examination was started with a calculation of the amount of the collected lavage fluid. A known volume of 1 ml phosphate buffered saline PBS pH 7.4 including 20% Mensa (UCB Pharmaceutics Company, Brussels, Belgium) was used to disrupt the disulphide bonds of mucus polypeptide. By counting the amount of cells in 1 cm^2 over a counting glass slide, it was possible to determine of the number of cells in the total collected volume. After that, the supernatant was removed, followed by re-suspension of the cell pellet in 1 ml PBS pH 7.2 containing 5% bovine serum albumin (BSA). The cells were washed with PBS / 1% BSA. Cytocentrifugation was carried out at a speed of 1200 rpm for 5 minutes. The cytocentrifuge–prepared smears were rapidly air-dried and stained using May-Grünwald-Giemsa. The stained preparations were examined under oil immersion at a 1000x magnification by light microscopy. A specialised morphologist who was blinded to the clinical picture, the examination and the investigation of the patient, counted three hundred cells and a differential count was obtained for each slide. In this study, the counted cells included neutrophils, eosinophils, basophils, lymphocytes, mononuclear cells and epithelial cells. The mononuclear cells included macrophages and monocytes.
For BALs, the authors considered eosinophilia at ≥1% and neutrophilia at ≥ 3% according to James et al. [10]. For MML, the authors considered eosinophilia at ≥ 4% according to Miller et al. [11] and neutrophilia at ≥ 5% according to Gill et al. [12].

Allergy assessment
The assessment was based on the presence of at least one positive skin test response to common allergens of the area, mea-

surement of allergen-specific IgE (Pharmacia-Upjohn, Uppsala, Sweden) or both, as well as total IgE.

Statistical analysis

It was performed using SPSS version 7.5 (SPSS, Inc, Chicago, IL). The authors analysed the cellular inflammatory changes in the upper and lower airways separately. Using Spearman's test inside each subgroup, MML cell differential counts, BAL cell differential counts and lower airways functional changes were correlated to each other. Additionally, using Wilcoxon signed rank tests; correlations of the previous parameters between different subgroups were obtained. Statistical significance was set at a p value = 0.05.

RESULTS

Lower airways assessment

According to the type of lower airways involvement, as determined using the subjective symptoms evaluation 6 patients were diagnosed as asthmatic and 19 patients were diagnosed as non-asthmatic.

Using the objective evaluation of the lower airways (PFT) in the non-asthmatic group, 9 patients were diagnosed as small airway disease (SAD) and 10 patients as normal lower airway (NLA).

So according to the previous subjective and objective parameters, the authors divided the patients into three subgroups:

- Asthma subgroup: among the 25 CRS patients, 6 (24%) met the criteria for the diagnosis of asthma, with the mean age being 46 years and the M: F ratio 4:2.
- Small airway disease (SAD) subgroup: the second subgroup included 9 patients (36%) who met the criteria of small airway disease the mean age was 44.8 y and the M: F ratio was 6:3.
- Normal lower airway (NLA) subgroup with no evidence of lower airways problems (no clinical history of lower airways problems, normal spirometry, no HBHR, and normal chest X-ray): it included 10 patients (40%) with normal spirometric function. Mean age in this subgroup was (38.7 years) and the M:F ratio was 8:2 (Table 1).

Middle meatal lavage (MML)

Table 2 shows the total and differential counts of 48 samples, as 2 samples were excluded from the NLA subgroup because of technical problems.

1. Total cell counts: no differences were observed between the three subgroups. The means of the left and right sides together were 56.5/cm^2 in asthma, 54.5/cm^2 in SAD, and 52/ cm^2 in normal lower airways (Table 2).
2. Cell differential counts: in this study, the cell differential count (CDC) means the percentage of each cell type of the total number of inflammatory cells (Table 2). There existed no significant difference between the left and right sides in different lower airways involvement subgroups; p>0.05.

a. The mean CDC for eosinophils was higher in the asthma subgroup (7.3%) than in the SAD and NLA subgroups (3% and 2.35% respectively). Using the Wilcoxon signed rank test, there was a significant difference for the eosinophils CDC between the asthma subgroup and the other two subgroups (p=0.028 and 0.046).

b. The mean CDC for neutrophils was higher in the SAD subgroup (8.7 %) than the other two subgroups (asthma subgroup 4.5% and NLA subgroup 4.45%). Using the Wilcoxon signed rank test there was a significant difference for the neutrophils CDC between the SAD subgroup and the other two subgroups (p=0.02 and 0.019).

c. No significant difference could be observed between the three subgroups concerning the mean CDC for basophils, lymphocytes, and monocytes (p> 0.05).

Table 1. Number, age, sex and smoking characteristics of CRS patients with different lower airways involvement subgroups.

	CRS Total no (25 patients)		
	Asthma	SAD	NLA
No of patients	6	9	10
Age (mean)	(35-66) 46	(25-54) 44,8	(31-52) 38,7
Sex M	4	6	8
Sex F	2	3	2
Smoking			
Active smoker n (%)	0	2(22%)	0
Ex-smoker n (%)	5(83.3%)*	1(11%)	0
Never smoked n (%)	1(16.7%)	6(67%)	10(100%)

*There existed a significant difference between asthma subgroup and the other subgroups concerning the ex-smoker (p=0.025). N.B. Fifty percent of asthma subgroup gave up smoking more than 20 years earlier. There existed no significant difference concerning the other factors.

N.B. SAD: small airway disease-NLA: normal lower airway.

Table 2. Mean values of middle meatal lavage (MML) cell differential count (CDC) and total absolute cell count (ACC/cm^3) of both sides in different lower airways involvement subgroups.

	CRS Group (25 patients) 48 Examined Samples		
Cell Type	Asthma	SAD	NLA
Neutrophils ± SD	4.5±3.6	8.7±9*	4.45±5.6
Eosinophils ± SD	7.3±3.8*	3±7.5	2.35±7
Basophils ± SD	0.5±4.8	0.11±0.3	0.27±0.6
Lymphocytes ± SD	8±4.5	9.9±9.5	6.71±10.3
Monocytes ± SD	3.96±4.3	2.7±3.4	3.3±5.2
Epithelial ± SD	75.5±7.4	75±12.5	83.4±15.8
Total ACC/cm3 ± SD	56±15.7	54±25	52±26.5

Eosinophilia can be shown in the asthma subgroup and neutrophilia in the SAD subgroup.

*Using the Wilcoxon signed rank test, there was a significant difference for the eosinophils CDC between the asthma subgroup and the other two subgroups (p=0.028 and 0.046).

*Using the Wilcoxon signed rank test, there was a significant difference for the neutrophils CDC between the SAD subgroup and the other two subgroups (p=0.02 and 0.019).

N.B. SAD: small airway disease-NLA: normal lower airway.

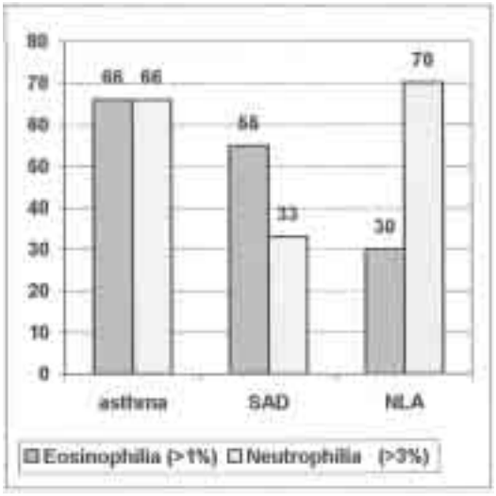

Figure 1. Percentage of patients with middle meatal nasal eosinophilia and neutrophilia.

If we consider every patient separately for eosinophilia and neutrophilia, the percentage of patients with significant eosinophilia was much higher in the asthma subgroup (83%) in comparison with the NLA subgroup (10%, p=0.025) but not the SAD subgroup.

On the other hand, the percentage of patients with neutrophilia was significantly higher in the SAD subgroup (77%; p=0.018) but not in the other two subgroups.

The frequency of nasal polyposis was significantly higher, up to 100%, in the asthma subgroup (p=0.038), while the frequency was 55% in the SAD subgroup and 30% in the NLA subgroup. The mean score on the right side was 1.3 in the asthma subgroup, 0.55 in the SAD subgroup and 0.3 in the NLA subgroup. On the left side, the mean score was higher in the asthma subgroup than in the other two subgroups: 1.3 in the asthma subgroup versus 0.55 and 0.7 in the SAD and NLA subgroups, respectively (p=0.004).

Bronchoalveolar lavage cytology (BAL)

Twenty-four samples of BAL were examined, as one sample in the NLA subgroup was excluded because of technical problems.

1. Total cell counts: there was no difference in the total number of cells in different subgroups (Table 3).
2. Cell differential count (CDC): the same definition of CDC as in MML was used in BAL:

a. For eosinophils: in the asthma subgroup, a significantly higher percentage of eosinophils (2.33%) was found as compared to the SAD and NLA subgroups (0.66% and 0.22%, respectively; p=0.046). Lung eosinophilia was observed in the asthma subgroup, but not in the other two subgroups.

b. For neutrophils: the mean percentage of neutrophils in asthma and NLA subgroups was higher; 6.5 % and 6.33% as compared to the SAD subgroup (2%; p>0.05).

Table 3. Bronchoalveolar lavage (BAL) mean cell differential count (CDC) and total absolute cell count (ACC /cm^2) in different lower airways involvement subgroups.

	CRS Group (25 patients) (24 examined samples)		
Cell Type	Asthma	SAD	NLA
Neutrophils±SD	6.3±9.6	2±1.5	6.5±8.6
Eosinophils±SD	2.3±3.3*	0.66±0.7	0.22±0.5
Basophils±SD	0.16±0.4	0.33±1	0.22±0.6
Lymphocytes±SD	18.5±12.6ß	5.44±2.3	7.77±7
Monocytes±SD	64.33±17.5	82.3±5.7	75.2±16.8
Epithelial±SD	8.5±5	8±3.8	10±7
Total ACC /cc±SD	269±252	243±193	276.6±240

*Using the Wilcoxon rank test, there was a significant difference in eosinophils between the asthma subgroup and the other subgroups (p=0.046). ß The statistical significance difference of lymphocytes in asthma was (p=0.06).
N.B. SAD: small airway disease-NLA: normal lower airway.

c. For lymphocytes: the mean CDC was (18.5%) in the asthma subgroup as compared to the other two subgroups (5.4 % and 7.7 %; p=0.06) (Table 3).

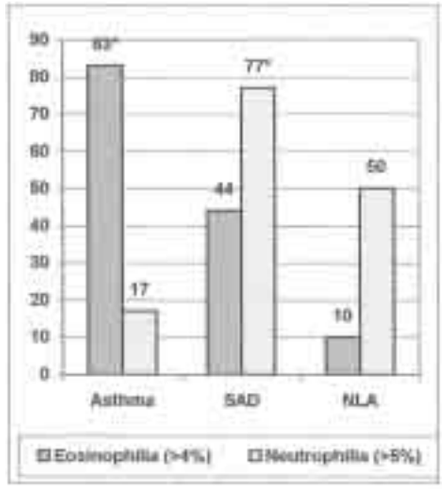

Figure 2. Percentage of patient with BAL eosinophilia and neutrophilia.

In the asthma subgroup, the percentage of patients with BAL eosinophilia and neutrophilia was 66% for each cell type. In the SAD subgroup, 55% of the patients had eosinophilia while 33% had neutrophilia. In the NLA subgroup, 30% had eosinophilia and 70% neutrophilia.

MML and BAL inflammatory cellular parameters and pulmonary function correlation between the different subgroups

For MML: using Spearman's test, in the asthma subgroup there was a significant negative correlation between MML eosinophils and FEV1 (p= 0.042). Also there was a significant negative correlation between MML eosinophils and the Tiffeneau index (FEV1/FVC) (p=0.037). In SAD subgroup, there was also a significant negative correlation between MML neutrophils on the one hand, and FEF75% and FEV1/FVC% on the other hand (p=0.013 and 0.012).

For BAL: there was no significant correlation between BAL cytological changes and pulmonary function changes ($p>0.05$).

No significant correlation was found between BAL and MML cellular changes ($p>0.05$).

Concerning atopy, there was no significant difference between the three subgroups. It was found in 4 (66%) in asthma, 5 (55%) in SAD and 4 (44%) in NLA.

DISCUSSION

This is the first study to compare cellular inflammatory changes of MMLs and BALs in CRS patients. Although various techniques have been used for obtaining cytological specimens, the technique that uses the examination of the nasal secretions is preferred [14]. With the technique used in this study, it was possible to easily obtain mucus samples with little trauma under endoscopic magnification. Furthermore, it is also similar to BAL, which is a well-standardised procedure in both clinical practice and research [5].

In chronic rhinosinusitis, different subsets of leukocytes are involved in the development of persistent inflammations of the nasal mucosa [15].

The role of eosinophils in chronic inflammatory diseases of the paranasal sinuses has been investigated with sinus tissue from patients with CRS. Marney [16] demonstrated increased numbers of eosinophils and increased levels of GM-CSF, IL-3 and IL-5 in biopsies of CRS compared with the controls. Different studies of sinus tissue in patients with CRS associated with asthma demonstrated more involvement of eosinophils [17,18]. Harlin et al., [17] demonstrated significant sinus tissue eosinophilia in all subjects of their group of 13 patients with CRS and asthma, in contrast to tissue eosinophilia in 6 of 13 patients with CRS without asthma. Hamilos [18] had also nearly similar observations where eosinophils dominated the inflammatory infiltrate in 10 of 21 patients with CRS, among whom 11 asthmatic patients were identified. The kinetics of eosinophils in nasal tissues and secretions are in fact far from well understood. The number of eosinophils found by Jankowski et al. [4] both in nasal secretion and polyp tissue was slightly but significantly correlated. This can explain the similarity of the predominance of mucus MML eosinophils in 83% of CRS patients with asthma between this study and the other previous tissue biopsy studies. In addition, Jankowski et al. [4] found that half the patients with CRS and asthma had high nasal mucus eosinophilia. Thus, this result appears to be less than in our study, due to the fact that mucus was collected only from the nasal cavity and not from middle meatus.

The role of eosinophils in asthma has been well documented [1]. Bronchial biopsies and BALs in asthmatics reveal activated CD4+ T lymphocytes, activated eosinophils and neutrophils in addition to the customary mast cells and alveolar macrophages [19,20]. The results of these studies are similar to our results showing mainly an increase of eosinophils with other inflammatory cells such as neutrophils, lymphocytes and basophils in BALs of asthma patient.

From the results of this study, a possible relation between MML eosinophils and asthma in CRS could be suggested. The eosinophilic inflammatory process in upper airways is dominated by a suspected increase of their toxic inflammatory products, such as MBP. Propagation of these toxic products to the lower airways either via the airway passages or via their absorption through the systemic circulation might induce or aggravate the inflammatory involvement of the lower airways. This relation can be explained by the following factors.

In this study, the asthmatic patients showed an increase of MML and BAL eosinophils. The effect of upper airways eosinophils over the lower airways can be highlighted through the correlation between the increase of eosinophils in the MML secretions and the abnormal pulmonary functions parameters (lower FEV1 and TI). This correlation was absent between the BAL eosinophils and these obstructive pulmonary function parameters. Also the pathologic similarities of CRS and asthma are well known [21]. The level of eosinophil mediators like MBP was found to be high in CRS [16] as well as in asthma [22]. Experimental studies of instillation of MBP into the trachea of guinea pigs augmented bronchoconstriction induced by intravenous acetylcholine [23]. Furthermore the role of mediator aspirations into the lower airways was strengthened in the Brugman study [24].

On the other hand, different other mechanisms were suggested previously to explain nose lung interactions in CRS, but also with multiple arguments against them.

For the associated inflammatory changes due to CRS and their propagation to the lower airways, there is no experimental information indicating that nasal inflammation in CRS leads to systemic inflammatory signals [25].

Braunstahl et al. [26] and other investigators [25,27] support the concept of nasobronchial reflex with delayed kinetics. The nasobronchial or pharyngobronchial neural reflexes, even if one accepts their role based on experimental evidence, are expected to be stimulated only upon intense acute stimulation. However, in CRS, it is a continuous inflammatory process. The failure, however, to control asthma using anticholinergic drugs in patients with CRS excludes this mechanism [20]. Though the fine details of the orchestration of airway neural activity have yet to be delineated, non-adrenergic non-cholinergic mechanisms may act [28]. For nasal obstruction, although

nasal obstruction can aggravate asthma, it could hardly be the only mechanism,as humidification provides moderate symptomatic relief only [20].

In contrast to the asthmatic subgroup, neutrophils seem to play a major role in CRS with small airways involvement. In this study, the SAD subgroup showed a higher neutrophil involvement of the paranasal sinus mucus than the other two subgroups of asthma and NLA. The role of the neutrophils in CRS was also determined in the Lee et al. study [29] in 123 patients with chronic sinusitis in whom cytology of the nasal secretion was performed. Suzuki et al. [30] also proposed the hypothesis of neutrophils recruitment in CRS aggravated by bacterial infections. Grevers et al. [15] confirmed these results with histological tissue examination of 14 patients with non-allergic CRS. They identified an increased density of neutrophils in CRS patients versus the control group. Neutrophils are not only the terminal effectors cells, they can also affect other cells releasing various cytokines such as IL-1α, IL-1β, IL-6, IL-8, interferon α and TNF which are able to activate B cells and T cells [15]. Additionally, accumulated neutrophils in sinus secretions probably release proteases and superoxides, which lead to more impairment of the mucociliary function with more aggravation of the inflammatory process [30]. In the SAD subgroup, the neutrophils in MMLs correlated with the obstructive lower airway parameters but not with lower airway neutrophilia. The absence of a corresponding increase in BAL neutrophils in this subgroup also highlighted the role of CRS neutrophil toxic products and mediators in these functional changes. Based on the above results, one can suggest a mechanism for sinonasal rhinosinusitis bronchiolar interactions in this subgroup of patients. The inflammatory cells in the upper airways were mainly neutrophils and by releasing their cytokines, they can affect the most dependent part of the respiratory tract, which are the bronchioles. One pathway could involve the propagation of the inflammation from the upper to the lower airways via the airways. That pathway was also identified in Brugman's et al. study [24] with a rabbit model of inflammatory sterile sinusitis. The development of sinusitis in that model is associated with a hyperresponsiveness of lower airways. The injection of complement fragments into the knee joint, in spite of inflammation induction, did not result in changes in the lower airway physiology. On the other hand, the sinusitis-induced lower airway hyperresponsiveness was eliminated by positioning the rabbit in such a way that airway secretion did not travel into the lower airways by way of gravity. In their experimental study, Corren et al. [31] also identified a neutrophil influx and activation in CRS and their association with airway hyperresponsiveness, and the presence of a small number of neutrophils in BAL fluid. Another possible pathway is via the blood, by absorption of spasmogens and mediators with their local effects over the lower airways in the bronchiolar part, which is devoid of cartilage support.

In conclusion, the authors found different inflammatory cells in the nasal secretions of CRS patients with different types of lower airway interactions. In asthma, eosinophils were the predominant cells in the MML, while in CRS with SAD, the predominant cells in MML nasal mucus were neutrophils. Both MML eosinophils in asthma and MML neutrophils in SAD correlated with lower airway obstructive pulmonary function changes. On the other hand, there was no significant correlation between the upper and lower airways cellular changes.

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SOCIETY NEWS

FELLOWSHIPS IN RHINOLOGY

Sponsored by

THE EUROPEAN RHINOLOGIC SOCIETY

Available to Trainee-Surgeons from Eastern Europe

One place available on each of the following Courses in 2004-2005

International Course on in Functional-Aesthetic Nasal Surgery
Ulm, Germany, March 8-11 2005
Course Director: Prof.Dr. G. Rettinger
Language: English

International Course in Functional Corrective Nasal Surgery
Utrecht, The Netherlands, June 14-17 2005
Course Director: Dr. A.F. van Olphen
Language: English

International Course on FESS (Basic and Advanced Techniques)
Graz, Austria, July 07-09 2005
Course Director: Prof.Dr. H. Stammberger
Language: English

An Endoscopic approach to Rhinosinusitis
London, United Kingdom, October 20-23 2004
Course Directors: Prof. V.J. Lund and I.S. Mackay
Language: English

6th International Course on Reconstructive and Aesthetic Surgery of the Nose and Face "Around the Nose"
Nijmegen, The Netherlands, May 18-20 2005
Language: English

Third Biennial International Milano Masterclass. Sinonasal and Skull Base Endoscopic Microsurgery, Advanced Rhinoplasty and Pearls of Facial Plastic Surgery, Milano March 3-9 2005
Course Directors: Prof. P. Castelnuovo and Prof. P. Palma
Language: English

Sponsorship comprises a sum of 1200 Euro to assist in both registration fees and costs of accommodation. Application forms are available from the Secretary of the ERS.
Applications should be submitted at least three months before the course starts. Applications and/or queries should be directed to either the President or the Secretary of the European Rhinologic Society.

Prof. M. Önerci (President ERS), Department of Otorhinolaryngology, Hacettepe University, Sihhiye - Ankara, Turkey

Prof. G. Rettinger (Secretary General ERS), Department of Otorhinolaryngology, University of Ulm, Prittwitzstrasse 43, D-89070 Ulm, Germany

ERS-members is given 10% reduction of the registration fee