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Assessment of inflammation in noninfectious chronic maxillary sinusitis

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Abstract

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Background and aim: Pathologic examination of the sinus mucosa and titration of inflammatory mediators in the sinus fluid were carried out to characterize inflammation in chronic sinusitis and determine whether patients with chronic allergic rhinitis (CAR) and sinusitis differ from patients with chronic nonallergic rhinitis (CNAR) and sinusitis.

Methods: Nine control subjects (patients requiring ear, nose, and throat surgery not related to sinusitis), 12 patients with CAR and sinusitis, and 13 patients with CNAR and sinusitis were investigated. Eosinophil cationic protein, tryptase, myeloperoxidase, histamine, and prostaglandin D₂ were measured in the sinus lavage fluids, and cells were enumerated. The cellular infiltrate was studied by immunohistochemistry with monoclonal antibodies against eosinophil cationic protein (eosinophils), tryptase (mast cells), neutrophil elastase (neutrophils), CD3 (lymphocytes), CD68 (macrophages), and proliferating cell nuclear antigens.

Results: Neutrophils were not increased in sinusitis. In comparison with control subjects, patients with CAR and CNAR with sinusitis showed significant increases in eosinophils and macrophages in biopsy specimens and in eosinophil cationic protein in sinus lavage fluids. In comparison with patients with CNAR, patients with CAR had an increased number of intraepithelial mast cells and lymphocytes.

Conclusions: These findings suggest that patients with CNAR and sinusitis can be distinguished from patients with CAR and sinusitis, which resembles nonallergic rhinitis with eosinophilia syndrome. (J ALLERGY CLIN IMMUNOL 1994;94:95-108.)

CAR Chronic allergic rhinitis

CNAR Chronic non-allergic rhinitis

ECP Eosinophil Cationic protein

mAb Monoclonal antibody

MBP Major basic protein

MPO Myeloperoxidase

PCNA Proliferating cell nuclear antigen

PGD₂ Prostaglandin

(Click on a term to search this journal for other articles containing that term.)

Key words: [Chronic sinusitis](#), [inflammation](#), [eosinophils](#), [mast cells](#), [neutrophils](#), [lymphocytes](#), [macrophages](#), [immunohistochemistry](#)

Sinusitis and nasal diseases are among the most frequent chronic diseases, with a high morbidity rate and economic cost.¹ Although acute sinusitis is often due to viral upper respiratory infections,² the causes of chronic sinusitis are usually less well defined. The relationships between sinusitis and allergy have been discussed for many years because of the high frequency of immediate-type hypersensitivity in patients with chronic sinusitis.^{3 5} However, it is not yet known whether “allergic sinusitis” can be distinguished as a specific entity. In chronic sinusitis eosinophils are common,⁶ and the disease may respond to treatment with corticosteroids.

Pathologic examination with immunohistochemical techniques and the analysis of inflammatory mediators have been widely used in bronchial and nasal mucosa samples obtained from normal subjects and patients.^{7 9} Such studies are still rare in chronic sinusitis, although recently, Harlin et al.¹⁰ have demonstrated a close association between the presence of extracellular major basic protein (MBP) and sinus mucosal damage. The lack of published data has been due to the difficulty in accessing the sinus mucosa. The recent advances in endoscopic paranasal sinus surgery should alleviate this problem.^{11 12}

Eosinophils are increased in number in allergic inflammation of the nose¹³ and lungs,⁷ but their presence is not specific for allergy, because some patients with chronic rhinitis have the so-called nonallergic rhinitis with eosinophilia syndrome.¹⁴ In allergic disorders other cells including mast cells, lymphocytes, macrophages, and to a lesser extent, neutrophils are involved, releasing proinflammatory mediators, as well as cytokines and growth factors.^{8 9}

The characterization of inflammatory cells involved in sinusitis can be carried out in biopsies with immunohistochemical methods that are more sensitive and specific than conventional histologic methods. Eosinophils can be enumerated with monoclonal antibodies (mAbs) against ECP that recognize resting and activated eosinophils^{15 16}; neutrophils can be identified with anti-elastase mAbs,¹⁷ mast cells with anti-tryptase mAb,¹⁸ lymphocytes with anti-CD3 antibody,¹⁹ and macrophages with anti-CD68 mAb.²⁰ When activated, cells release mediators and proteins, which may be specific for a cell type and can be measured in body fluids. For eosinophils, ECP and MBP are the most widely used.^{7 16} For the basophil–mast cell lineage, histamine, tryptase, and prostaglandin D₂ (PGD₂) are measured.²¹ Mast cells and basophils can be discriminated by their granule or secretory products; mast cells, in contradistinction to basophils, release tryptase and PGD₂.^{21 22} Neutrophils release myeloperoxidase (MPO), which can be specifically measured in fluids.²³

In an attempt to examine inflammation in chronic sinusitis and to distinguish patients with allergic sinusitis and from those with nonallergic sinusitis, 12 patients with sinusitis and chronic allergic rhinitis (CAR) and 13 patients with sinusitis and chronic nonallergic rhinitis (CNAR) were compared with nine control subjects who required ear, nose, and throat surgery not related to sinusitis. We examined the inflammation caused by eosinophils, neutrophils, mast cells, macrophages, and lymphocytes by immunohistochemistry on surgical specimens, immunocytochemistry on sinus

lavage fluids, and measurement of specific inflammatory mediators in the sinus lavage fluids.

Methods

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Study subjects

Thirty-four subjects, 19 men and 15 women, entered the study prospectively between August 1990 and April 1991. Twenty-five patients, ranging in age from 17 to 68 years (mean $\pm$ SD, 39 ± 16 years), had nasal symptoms (e.g., nasal obstruction, rhinorrhea) at the time of the surgery, which had failed to respond to optimal medical treatment, as outlined by Druce and Slavin.¹¹ Patients were excluded from the study if they had taken systemic corticosteroids during the 2 months before the surgery or nasal corticosteroids during the previous month. None had had any clinically demonstrable ear, nose, and throat infection during the month preceding the surgery or a history and physical examination suggesting a diagnosis of chronic bronchitis or cystic fibrosis. Patients allergic to pollen underwent surgery out of the pollen season. Eight percent of the patients were current smokers.

Nine subjects, ranging in age from 16 to 63 years (mean $\pm$ SD, 44 ± 17 years), were used as a control group. They were nonallergic and had never had chronic rhinitis or sinusitis. No subject had had any ear, nose, and throat infection during the month preceding the study. They underwent surgery for various reasons: carcinoma of the larynx (four), laryngeal polyposis (one), and rhinoplasty (four).

The study was done only after informed consent was obtained and approval of the Ethics Committee of the Hospital was given.

Sinus and allergologic investigations

Diagnosis of sinusitis

All subjects underwent identical sinus investigations. An inquiry regarding purulent nasal and postnasal discharge, nasal obstruction, facial headache, hyposmia, chronic cough, and halitosis was obtained. Anterior rhinoscopy was performed for signs of mucopurulent discharge, nasal hyperemia, nasal edema, nasal polyposis, or nasal anatomic abnormalities (e.g., septal deviation). Plain paranasal sinus radiographs including occipitofrontal (Caldwell), occipitomenal (Waters), and lateral views were taken. Computed tomography scans (in the anteroposterior and coronal planes at 1 cm intervals) were obtained. They were carried out with a fourth-generation scanner (CGR CE 12000; Siemens, Munich, Germany) with bone window settings.

The diagnosis of chronic sinusitis was based on the modified criteria of Druce and Slavin,¹¹ as one or more suggestive symptoms of chronic sinusitis described above occurring more than three times a year for at least 2 years and an abnormal imaging examination with evidence of mucoperiosteal thickening (>6 mm) of maxillary sinuses.

Diagnosis of immediate-type hypersensitivity

All subjects underwent identical investigations. The onset, duration, and recurrence of symptoms were carefully checked. Skin prick tests with extracts of the common food allergens and aeroallergens found in the Montpellier area²⁴ were performed. Total serum IgE (with Phadebas paper radiosorbent test and Phadiatop; Pharmacia Diagnostics AB, Uppsala, Sweden)²⁵ was determined. Serum-specific IgE was titrated by the Phadebas RAST (Pharmacia Diagnostics AB) in patients with positive skin prick test results.

Patients were considered to have perennial allergic rhinitis when there was: (1) a suggestive history (i.e., nasal allergic symptoms occurring at the same time in the year, each year for several years, or perennial nasal allergic symptoms with exacerbations occurring each year for several years during the fall) and (2) the demonstration of an allergy to perennial allergens by skin prick test results and serum-specific IgE antibodies corresponding to the chronology of symptoms.

Patients were considered to have perennial nonallergic rhinitis when: (1) the chronology of nasal symptoms did not fit an allergy to the perennial allergens of our area, (2) skin prick test results were negative, and (3) Phadiatop results were negative.

Endoscopy of the nose and maxillary sinus

Endoscopy was performed with a 30-degree angle-viewing 4.00 mm Storz Hopkins rigid endoscope (Storz, Tuttlingen, Germany) after preparation of the nose with a solution of 5% lidocaine and 0.02% naphazoline. The procedure began with examination of the nose, focusing on the middle meatus. Then after antrostomy was performed through the inferior meatus, the endoscope was introduced into the maxillary sinus cavity. The antrum was then inspected with 30-, 70-, and 120-degree Storz Hopkins rigid endoscopes. Pathologic abnormalities were noted. A lavage of the sinus was subsequently done with 10 ml of saline solution. A sample of the fluid was aseptically collected for anaerobic and aerobic bacteriologic and fungal analyses according to standard methods described elsewhere.^{26, 27} Finally, a biopsy of the sinus was performed with alligator forceps. The duration of the procedure ranged from 5 to 15 minutes.

Measurements of mediators in sinus lavage fluid

Eosinophil cationic protein (ECP) was titrated in sinus lavage fluid by a double antibody radioimmunoassay (Pharmacia Diagnostics AB) with a polyclonal rabbit antibody, as previously described by Venge et al.²⁸ The ECP standards are calibrated against pure ECP prepared according to the method of Peterson et al.²⁹ The intraassay and interassay coefficients of variation are under 12%, and levels under 2 µg/L are undetectable.

Tryptase was titrated in sinus lavage with a commercially available kit (Pharmacia Diagnostics AB) based on two tryptase specific mAbs.^{30, 31} The intraassay and interassay coefficients of variation are less than 4% for samples. Levels of tryptase under 0.5 µg/L are undetectable,³² and the tryptase standards are calibrated against pure tryptase prepared by immunoaffinity chromatography, as described previously.³¹

MPO was titrated with a double antibody of radioimmunoassay as recommended by the manufacturer (Pharmacia Diagnostics AB). MPO in samples competes with a fixed amount of iodine 125–labeled MPO for the binding sites of a specific polyclonal rabbit antibody. The interassay coefficient of variation is under 13%, and levels under 8 µg/L are undetectable.²³

Histamine was titrated by radioimmunoassay with an mAb against acylated histamine (Immunotech, Marseille, France),³³ and the limit of detectability is 4.5 nmol/L.

Prostaglandin D₂ (PGD₂) was assayed by enzyme immunoassay according to the method of Maclouf et al.³⁴ with acetylcholinesterase from the electric eel as the enzyme.³⁵ The technique used is commercially available (Stallergènes Laboratories, Fresnes, France). The limit of detectability is 30 pg/ml.

Enumeration of cells in sinus lavage fluid and immunocytochemistry

Cytocentrifuge preparations from the sinus lavage fluids, containing 10⁵ cells each, were fixed in methanol/acetone (1:1, vol/vol) and rehydrated before further examination. One slide was stained with Diff-Quick (Baxter Healthcare Corp., Scientific Div., McGaw Park, Ill.) (May-Grünwald-Giemsa–derived method) for differential counts. For immunocytochemistry, two primary mouse mAbs were used (■Table I): anti-tryptase G3 (mast cells),¹⁸ and anti-neutrophil elastase NP57 (Dako, Glostrup, Denmark).¹⁷ The percentage of positive cells was assessed with immune complexes of alkaline phosphatase and monoclonal anti-alkaline phosphatase.³⁶ Briefly, the primary mAb (final dilution, 1:25) was incubated for 30 minutes at 37° C in humid chambers. Slides were washed three times in Tris-buffered saline solution (10 minutes each) and then incubated for 30 minutes with a rabbit anti-mouse IgG (final dilution, 1:100) (Dako). Slides were again washed three times and then incubated with the alkaline phosphatase–anti-alkaline phosphatase antibody (final dilution, 1:50) (Dako); finally, the alkaline phosphatase substrate, mixed with the indicator Fast Red dye (Dako), was added. The slides were washed, counterstained with hematoxylin, and mounted in Glycergel (Dako). Control slides were prepared by using an irrelevant mouse antibody of the same isotype at the same concentration as the specific primary mAb (Dako). Two different investigators, who were both unaware of the clinical findings, examined the slides. Positive (red) cells were counted with the use of a high power field.

TABLE I. Panel of antibodies used to characterize sinus mucosa

Antibody	Type of antibody	Specificity	Cells	Source	References
EG1	Mouse monoclonal	Human ECP	Eosinophils	Pharmacia	15,16
EG2	Mouse monoclonal	Human ECP	Eosinophils	Pharmacia	15,16
NP57	Mouse monoclonal	Human neutrophil elastase	Neutrophils	Dako	17
G3	Mouse monoclonal	Human tryptase	Mast cells	L. B. Schwartz	18

PG-M1	Mouse monoclonal	Human CD68	Macrophages	Dako	Unpublished
CD3	Rabbit polyclonal	Human CD3	T cells	Dako	19
PC10	Mouse monoclonal	Human PCNA	Cycling cells	Dako	38

Pathologic examination of sinus mucosa and immunohistochemistry

Biopsy specimens were fixed in 3.7% weight by volume formaldehyde and embedded in paraffin blocks. Four micrometer sections were deparaffinized and rehydrated before immunohistochemistry was performed. A first section was stained with hematoxylin and eosin for routine histologic evaluation. The following mAbs were used in this study (■Table I): (1) anti-ECP EG1 and EG2 (Pharmacia Diagnostics AB),^{15 16} (2) anti-neutrophil elastase NP57 (Dako),¹⁷ (3) antitryptase G3,⁸ (4) anti-macrophage CD68 (PG-M1, Dako),²⁰ (5) anti-T cell CD3 (Dako) (whole set of T-lymphoid cells),¹⁹ (6) anti-proliferating cell nuclear antigen (cyclin) PC10 (Dako) examining proliferating cells.³⁷ The percentage of positive cells was assessed with the biotin-streptavidin-peroxidase system (Dako LSAB).³⁸ Sections were incubated sequentially with the following reagents for 30 minutes at room temperature and rinsed in phosphate-buffered saline after each incubation. Briefly, after endogenous peroxidase was blocked with 3% hydrogen peroxide followed by incubation with nonimmune goat serum, slides were incubated with the primary mAb (at dilutions of 1:10 to 1:50). Slides were then incubated sequentially with 1:100 biotinylated sheep anti-mouse immunoglobulins, 1:200 peroxidase-conjugated streptavidin, and 3-amino-9-ethylcarbazole containing hydrogen peroxide. Slides were counterstained with hematoxylin and mounted in Glycergel. Control slides were prepared as described above. Two different investigators, both unaware of the clinical findings, examined the slides. Positive (red-brown) cells were counted per square millimeter with a high power field by superimposing a grid of 0.05 mm² on the sections. Quantitative results are expressed as means of measurements of 5 to 10 randomly chosen areas. The degree of extracellular staining was graded as 0 (negative cells), 1 (positive cells without any extracellular staining), 2 (extracellular staining with discernible cytoplasm) and 3 (intense extracellular staining throughout the lesion with no discernible cytoplasm). Positive nuclei (proliferating cell nuclear antigen [PCNA] immunoreactivity) and intraepithelial mast cells were counted per 100 μ m of basement membrane surface (as means of 5 to 10 measurements). PCNA immunostaining intensity was graded as + + + (very bright), + + (moderate), + (faint), or - (absent).

Statistical analysis

The Kruskal-Wallis test and Mann-Whitney U test with Bonferroni's correction were used for statistical comparisons among the three groups. Results are given as means $\pm$ SD, except for ECP and MPO levels, which are given as medians and ranges because of values under the limit of detectability.

Results

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Patients

Characteristics of the patients are described in ■ Table II. Twelve patients who had sinusitis with CAR age range, 17 to 63 years; (mean $\pm$ SD, 33 $\pm$ 16 years) took part in the study. Thirteen patients who had sinusitis with CNAR age range, 20 to 68 years; (mean $\pm$ SD, 45 $\pm$ 15 years) were also investigated. None of the patients had a history of aspirin intolerance. Six patients had asthma (four in the CAR group and two in the CNAR group). By endoscopic examination and computed tomography scans it was observed that none of the patients had nasal polyposis or anatomic obstruction of the paranasal sinuses. The endoscopic examination of the maxillary sinus showed mucosal hyperemia (data not shown) in all cases. Results of bacteriologic and fungal analyses were all negative, and no subject was excluded for this reason. There was no macroscopic bleeding during endoscopy.

TABLE II. Patient characteristics

Subjects (<i>n</i> = 4)	Age (yr)	Sex	Allergy	Serum IgE (U/L)
Control subjects (<i>n</i> = 9)				
1	63	M	—	27
2	16	F	—	46
3	53	F	—	19
4	23	F	—	54
5	63	M	—	98
6	61	F	—	5
7	41	F	—	15
8	42	M	—	37
9	39	M	—	55
Mean $\pm$ SD	44 $\pm$ 17			
Median	—	—	—	37.0
Patients with sinusitis and CAR (<i>n</i> = 12)				
10	17	M	P	142
11	44	M	P	37
12	51	M	Dp, P	31
13	19	M	P, M	189
14	29	F	Dp, P, C	269
15	22	M	Dp, P, M	192
16	17	M	P	590
17	41	M	Dp, P	95
18	29	M	Dp, P	132
19	17	M	P	328

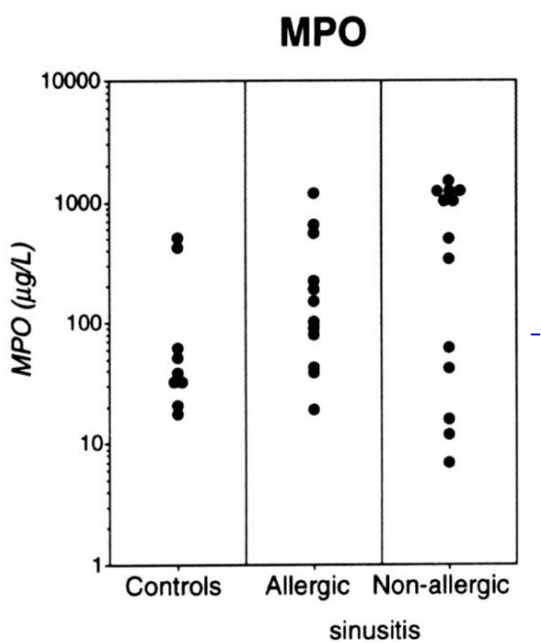
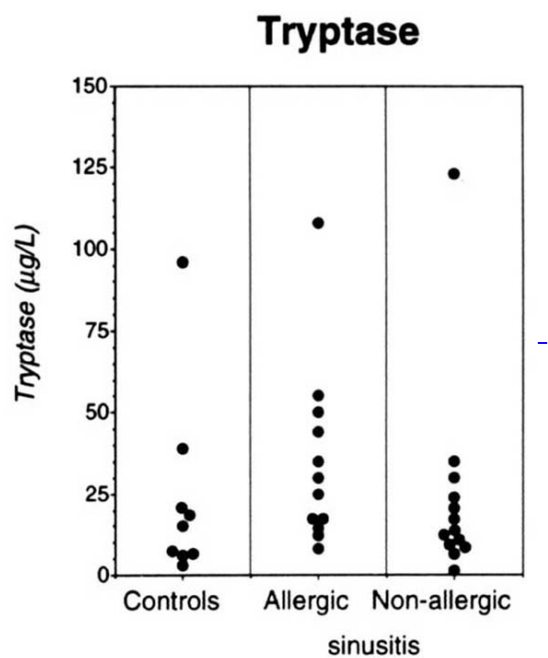
20	49	F	P, M	151
21	63	F	Dp	594
Mean ± SD	33 ± 16			
Median	—	—	—	170.2
Patients with sinusitis and CNAR (n= 13)				
22	42	M	—	63
23	64	F	—	45
24	42	M	—	27
25	38	F	—	47
26	28	F	—	19
27	57	F	—	54
28	67	M	—	963
29	25	M	—	269
30	32	M	—	38
31	58	F	—	45
32	32	F	—	174
33	38	F	—	0
34	68	M	—	102
Mean ± SD	45 ± 15			
Median	—	—	—	49.5

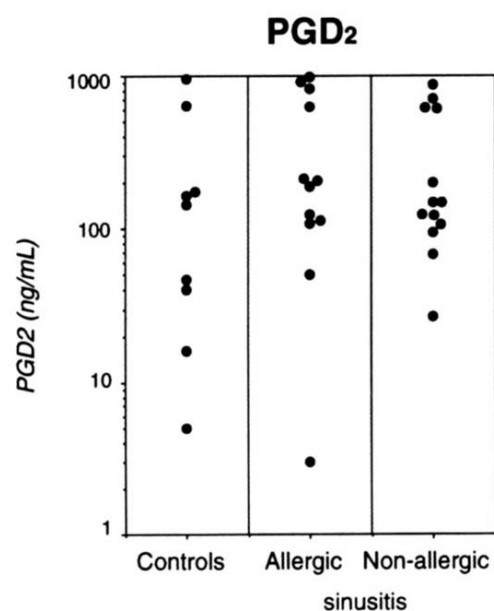
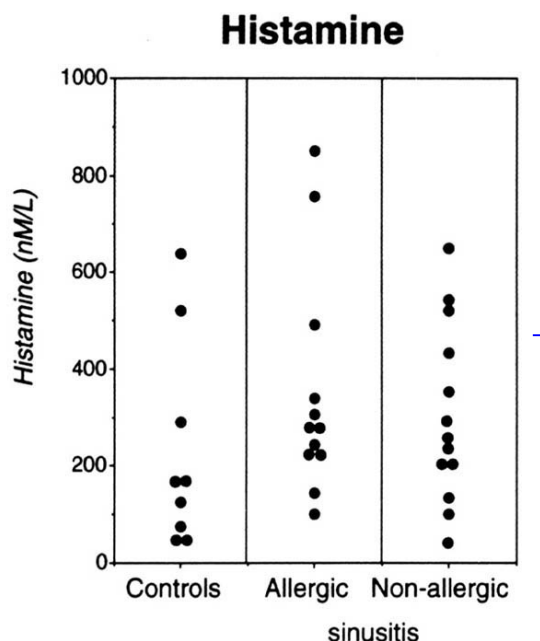
Dp, *Dermatophagoides pteronyssinus*; M, molds; P, pollen; C, cat.

Sinus lavage mediators

According to the Kruskal-Wallis test, the only significant difference between groups was observed for ECP levels ($p = 0.01$). Results are given in ■ Tables III and IV and ■ Fig. 1. The ECP levels in sinus lavage fluids were significantly greater in patients with CAR with sinusitis ($p = 0.0004$) than in control subjects. There was no significant difference between CAR with sinusitis and CNAR with sinusitis. There was no difference in patients with or without asthma. The MPO levels in sinus lavage fluids were not significantly increased in patients with CAR and sinusitis or patients with CNAR and sinusitis. The histamine, tryptase, and PGD₂ levels in sinus lavage fluids were similar in the three groups.

FIG. 1. Levels of ECP, histamine, MPO, tryptase, and PGD₂ in sinus lavage fluids from patients with sinusitis and chronic allergic and nonallergic rhinitis and control subjects.





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Sinus lavage cells

Red blood cells were found in all slides. Differential counts of sinus lavage cells are presented in Tables III and IV. There was a good correlation between the counts of the two investigators. According to the Kruskal-Wallis test, the only significant differences among the three groups were observed for eosinophils ($p = 0.0008$) and mast cells ($p = 0.01$). The percentage of eosinophils was significantly greater in patients with CAR and sinusitis ($p < 0.0005$) than in control subjects (no eosinophils); moreover, percentages for patients with allergic and nonallergic rhinitis were significantly different ($p < 0.015$). The percentage of mast cells was significantly greater in the patients with CAR and sinusitis and in those with CNAR and sinusitis ($p = 0.008$ and $p = 0.005$, respectively) than in the control subjects (no mast cells). The percentage of neutrophils was not significantly greater in the patients with CAR and sinusitis and the patients with CNAR and sinusitis than in the control subjects. Over 98% of neutrophils were stained by the mAb anti-elastase NP-57, with frequent extracellular staining. The mean percentages of epithelial cells and mononuclear cells

were similar in the three groups.

Pathologic examination of the biopsy specimens with hematoxylin and eosin staining

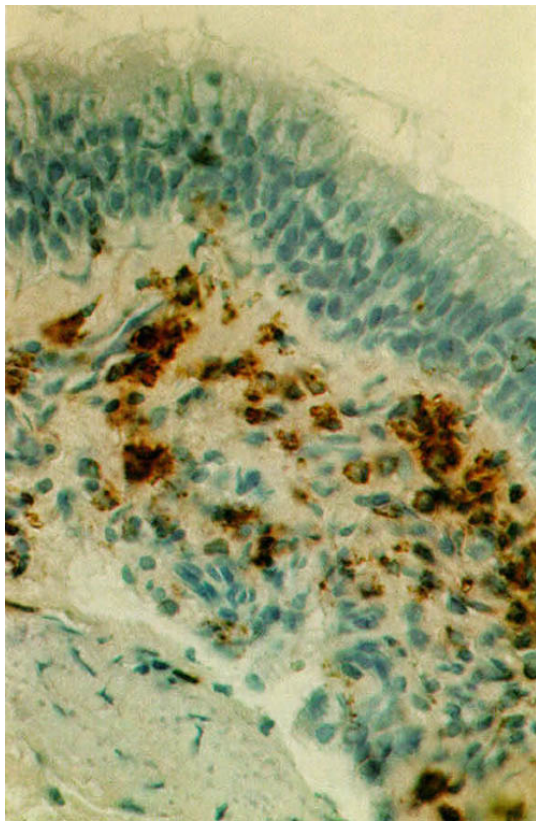
There was a good correlation between the counts of the two investigators. The surface area of the sections ranged from 0.25 to 2.50 mm². The epithelium was a typical pseudostratified ciliated epithelium with goblet cells and a relatively cell-rich submucosa (subepithelial layer). Epithelial shedding was present in parts (less than 20% of the total epithelium surface) of the sections in about 50% of the subjects in all three groups, and we carefully avoided examination of edges of the biopsy specimens, which apparently contained artifacts caused by forceps. Edema was found in 3 of 9 control subjects, 11 of 12 patients with CAR and sinusitis and 13 of 13 patients with CNAR and sinusitis. None of control subjects had thickened basement membranes compared with 5 of 12 patients with CAR and sinusitis and 2 of 13 patients with CNAR and sinusitis. Twenty-two patients with chronic sinusitis (88% vs. 1 of 9 control subjects) had submucosal inflammatory infiltrates (approximately 2 times more cells than control subjects) made up of different cell types, among which polymorphonuclear cells were the most recognizable. Neutrophils were only present in the submucosal blood vessels of four patients, and eosinophils were present throughout the epithelium in 6 of 25 patients with chronic sinusitis (data not shown).

Immunohistochemistry

According to the Kruskal-Wallis test, significant differences between groups were observed for EG1 ($p = 0.01$) and EG2 mAbs ($p = 0.04$), submucosal ($p = 0.03$) and intraepithelial mast cells ($p = 0.002$), and anti-CD68 ($p = 0.002$) and anti-CD3 mAbs ($p = 0.047$). Results are given in ■ Tables III and IV and ■ Figs. 2, ■3, ■4, ■5 and ■6.

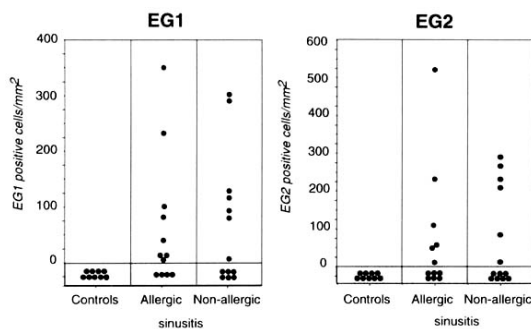
Eosinophils were found in significantly greater numbers in patients with CAR and sinusitis ($p = 0.003$ and 0.01 for EG1 and EG2, respectively) and patients with CNAR and sinusitis ($p = 0.01$ for EG1) by comparison with control subjects (no staining). However, there was no significant difference between patient groups. Eosinophils were localized within and beneath the epithelium, as aggregates (■ Figs. 2 and ■3). Extracellular staining, suggesting exocytosis of granule protein, was frequently observed in both groups of patients with chronic sinusitis without any difference in the degranulation score (data not shown). Although these cells were frequently degranulated, there was usually no shedding of the epithelium. The six patients with asthma did not show any difference in eosinophil density.

FIG. 2. Immunohistochemical analysis of ECP (EG1) in a patient with sinusitis and CAR. (Original magnification $\times 400$.)



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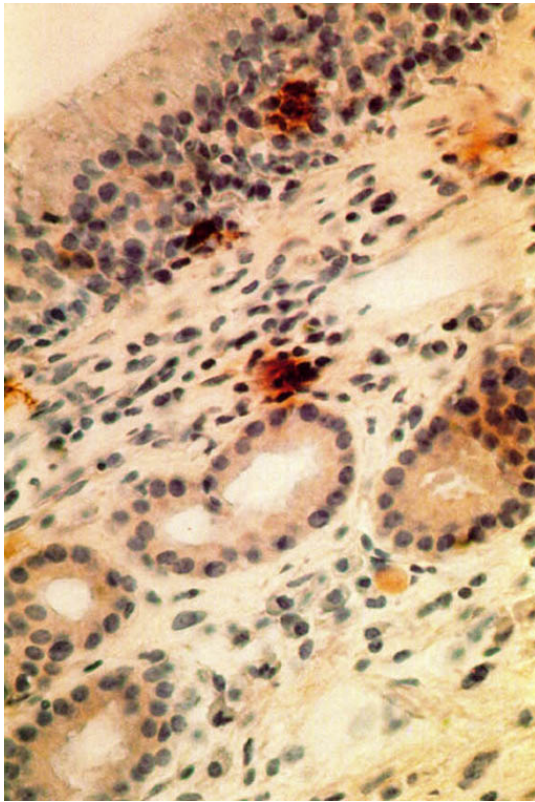
FIG. 3. Eosinophils (EG1- and EG2-positive cells) in sinus biopsy specimens of patients with sinusitis and chronic allergic and nonallergic rhinitis and control subjects.



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Mast cells were significantly increased in patients with CAR and sinusitis in comparison with patients with CNAR and sinusitis ($p = 0.015$) and were not significantly increased in comparison with those of control subjects (■ Figs. 4 and ■ 5). Mast cells were observed in the submucosa from 32 of 34 subjects, beneath the basement membrane and very often in perivascular areas. Intraepithelial mast cells were found in 10 of 12 patients with CAR and sinusitis, 2 of 9 control subjects, and 6 of 13 patients with CNAR and sinusitis. Degranulated submucosal mast cells, as demonstrated by extracellular tryptase staining, were occasionally observed in the three patient groups, with no intergroup difference in the degranulation score (data not shown). The six patients with asthma did not show any particularities.

FIG. 4. Immunohistochemical analysis of tryptase (G3) in a patient with sinusitis and CAR. (Original magnification $\times 400$.)

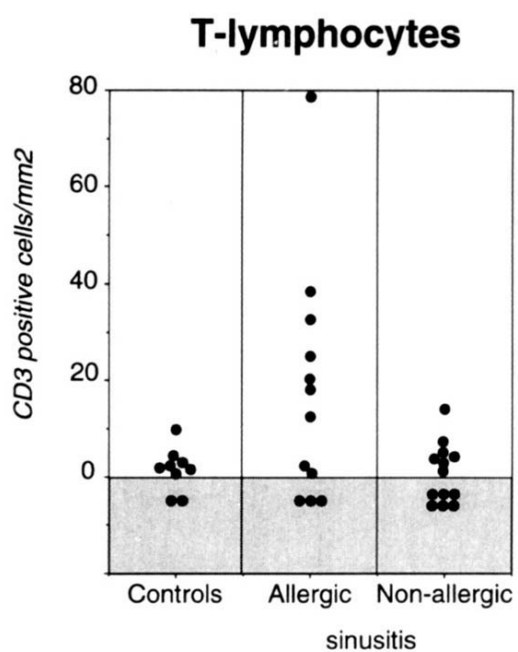
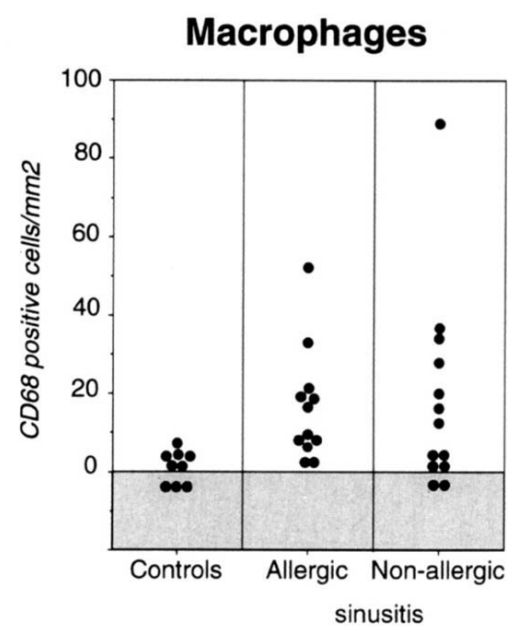


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FIG. 5. Mast cells in the submucosa and intraepithelium (G3-positive cells) in patients with sinusitis and chronic allergic and nonallergic rhinitis and control subjects.



FIG. 6. Neutrophils (elastase), macrophages (CD68), and T cells (CD3) in sinus biopsy specimens of patients with sinusitis and chronic allergic and nonallergic rhinitis and control subjects.



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Lymphocytes were increased in patients with CAR and sinusitis, not significantly in comparison with control subjects and significantly in comparison with patients with CNAR and sinusitis ($p = 0.015$). The majority of lymphocytes appeared as single cells or small aggregates in the submucosa and rarely infiltrated the epithelium, irrespective of the subject group (■ Fig. 6).

Neutrophils were rarely found, with no significant difference among the three groups (■ Fig. 6).

Some basal cells were positive for PCNA immunoreactivity in 0 of 9 control subjects, 5 of 12 patients with CAR and sinusitis and 4 of 3 patients with CNAR and sinusitis. Results are given in ■ Table III as means $\pm$ SD of positive nuclei per 100 μm of basement membrane. The staining intensity ranged from + to + + +. Very few positive cells were observed in the submucosal compartment.

TABLE III. Assessment of cellular inflammation in 25 patients with chronic sinusitis by comparison with nine control subjects

	Control subjects (n= 9)	Patients with allergic rhinitis (n= 12)	Patients with nonallergic rhinitis (n= 13)
Mediators in sinus lavage fluids			
ECP ($\mu\text{g/L}$)*	2, [2, 20]	17.5, [6, 180]	13, [2, 250]
Myeloperoxidase ($\mu\text{g/L}$)*	39, [17.5, 514]	174, [19, 1200]	501, [8, 1200]
Histamine (nmol/L)†	231 $\pm$ 214	355 $\pm$ 231	305 $\pm$ 184
Tryptase ($\mu\text{g/L}$)†	24 $\pm$ 29	35 $\pm$ 28	24 $\pm$ 31
PGD ₂ (ng/mL)†	0.24 $\pm$ 0.33	0.39 $\pm$ 0.41	0.30 $\pm$ 0.30
Cells in sinus lavage fluid†			
Epithelial cells (%)	63 $\pm$ 33	50 $\pm$ 20	43 $\pm$ 34
Polymorphonuclear cells (%)	28 $\pm$ 30	33 $\pm$ 19	49 $\pm$ 34
Mononuclear cells (%)	9 $\pm$ 7	13 $\pm$ 10	7 $\pm$ 7
Eosinophils (%)	0	4 $\pm$ 5	1 $\pm$ 2
Mast cells (%)	0	2.7 $\pm$ 3.4	2 $\pm$ 2.7
Immunohistochemistry†			
EG1 (per mm ²)	0	69 $\pm$ 110	78 $\pm$ 108
EG2 (per mm ²)	0	80 $\pm$ 154	84 $\pm$ 118
G3 (per mm ²)	55 $\pm$ 26	125 $\pm$ 91	41 $\pm$ 33
Intraepithelial G3 (per 100 μm basement membrane)	0.1 $\pm$ 0.3	0.7 $\pm$ 0.5	0.3 $\pm$ 0.4
Elastase (NP57) (per mm ²)	1 $\pm$ 1.2	9 $\pm$ 17	8 $\pm$ 17

CD68 (per mm ²)	1.5 ± 2	16.5 ± 14	19 ± 25
CD3 (per mm ²)	2.7 ± 3	20 ± 22	2.6 ± 4
PCNA (per 100 µm basement membrane)	0	0.7 ± 1.5	0.26 ± 0.40
*Median and range.			
†Mean ± SD.			

TABLE IV. Statistical results

Mann-Whitney U test with Bonerroni's correction				
	Kruskal-Wallis test	Control subjects vspatients with allergic rhinitis	Control subjects vspatients with nonallergic rhinitis	Patients wiht allergic and nonallergic rhinitis
Mediators in SLF				
ECP	0.01	0.004	NS	NS
Myeloperoxidase	NS			
Histamine	NS			
Tryptase	NS			
PGD ₂	NS			
Cells in SLF				
Epithelial cells	NS			
Polymorphonuclear cells	NS			
Mononuclear cells	NS			
Eosinophils	0.0008	0.0005	NS	0.015
Mast cells	0.01	0.008	0.005	NS
Immunohistochemistry				
EG1	0.01	0.003	0.01	NS
EG2	0.04	0.016	NS	NS
G3	0.03	NS	NS	NS
Intrapithelial G3	0.01	0.008	NS	NS
Elastase (NP57	NS			
CD68	0.002	0.0002	0.015	NS
CD3	0.047	NS	NS	0.015
PCNA	NS			

SLF, Sinus lavage fluids; NS, No statistical significance.

Discussion

TOP

This study shows that the infiltration of the sinus mucosa by activated eosinophils and macrophages is a feature of patients with allergic and nonallergic chronic rhinitis who have sinusitis, and allergic patients differ from the nonallergic ones by the presence of T cells and intraepithelial mast cells. Thus allergic sinusitis can be distinguished from nonallergic sinusitis.

The diagnosis of chronic sinusitis is difficult because it may be asymptomatic or have few symptoms. We based our diagnosis of sinusitis on positive computed tomography scans because standard radiography may underdiagnose the condition.^{11, 12, 39} We based our diagnosis of chronicity on the criteria of Druce and Slavin¹¹; that is, all patients were seen at least three times a year with recurrent suggestive symptoms of sinusitis verified by positive radiologic findings. The indication for surgery in our patients was recurrence of symptoms unresponsive to aggressive medical management. Bacterial and fungal infections were excluded by careful evaluation. Discolored mucus is not necessarily an indication of infection, and we assessed infection by using an appropriate culture.^{26, 27, 40, 41}

One of the other pitfalls that might be suggested by this study is the diagnosis of allergy in patients who are first seen with chronic rhinitis. When low-potency extracts are used, skin prick tests are less sensitive and reproducible than intradermal tests.⁴² With standardized extracts the prick test appears to be sensitive enough, and this method has been recommended for research purposes.^{43, 44} It is believed that the prick test results correlate better with symptoms, although in patients with a low sensitivity, intradermal skin tests may have the only positive results. All patients had a Phadiatop test to confirm the results of skin prick tests.²⁵ Moreover, the chronology of symptoms clearly differentiates patients with allergic rhinitis from those with nonallergic rhinitis. Thus it is likely that all patients were correctly classified.

The inflammatory mediators that we measured in the sinus lavage fluids of our patients are widely accepted as markers of inflammation in asthma and rhinitis. They can all be measured by sensitive and specific immunoassays, which are commercially available.^{7, 15, 23} However, blood vessel effraction cannot be avoided in ear, nose, and throat endoscopic surgery and is indeed a source of nonlocally produced mediators and blood cells.

We used paraffin-embedded biopsy specimens because of the better morphologic preservation of the sections.¹⁹ The mAbs were chosen according to their specificity against major inflammatory cells and the fixation procedure. EG1 stains 74% of resting eosinophils and 78% of activated eosinophils in the blood; EG2 recognizes 15% and 75% of resting and activated blood eosinophils, respectively; whereas anti-MBP mAb stains over 98% of eosinophils, irrespective of their degree of activation.¹⁶ However, this antibody was not readily available, and we used EG1 and EG2 mAbs. Neutrophil elastase (NP57) stains 98% of resting and activated blood neutrophils (personal data).

Although we titrated neutrophil MPO in the sinus lavage fluid, we did not use an mAb against neutrophil MPO because it cannot be used in paraffin-embedded sections. Tryptase staining provides a useful method of assessing mast cell infiltration in mucosa. G3 is a highly specific anti-tryptase mouse mAb, which stains all mast cells.¹⁸ In nasal polyps mast cells are more easily identified by immunohistochemistry than by staining with toluidine blue and alcian blue,⁴⁵ whereas mature basophils are stained by these dyes but not by G3.²² mAb anti-CD68, clone PG-M1, is directed against a cytoplasmic epitope present on most if not all macrophages. It can therefore be considered as a panmacrophage marker. In contrast to the clone PG-M1, clones KP-1 or EBM11 of CD-68 react with granulocytes.²⁰ Antibodies directed against CD3 ϵ -chain stain all normal and malignant cells of the T-lymphoid lineage.¹⁹

Eosinophils represent a key cell of the mucosal inflammation in rhinitis and asthma, but it has never been possible to differentiate allergic and nonallergic subjects on the basis of eosinophils or their granule proteins.^{7 9 14} In sinusitis although fewer studies have been performed, the presence of eosinophils was described by Hansel et al.⁶ in 1929. In two studies in which an anti-MBP mAb was used, a close association was demonstrated between the presence of extracellular MBP and damage of sinus mucosa in one of the two studies performed.^{10 46} However, in these two studies the causes of the sinus disease were not fully determined, and control subjects were not included. In the present study we compared patients with and without sinusitis and found activated eosinophils in the mucosa of patients with chronic sinusitis, irrespective of their allergic status. These observations were substantiated by the presence of increased levels of ECP in the sinus lavage fluids. Thus patients with nonallergic sinusitis resemble those with nonallergic rhinitis with eosinophilia syndrome and cannot be differentiated from those with allergic sinusitis on the basis of eosinophilic inflammation. In the present study and in contradistinction to previous studies in asthma,^{7 9} we did not find any obvious epithelial damage in patients with degranulated eosinophils. Thus eosinophils may be necessary but not sufficient for epithelial damage, as has been suggested by Hisamatu et al.⁴⁷ The origin of eosinophils in the sinus mucosa is associated with mRNA expression of granulocyte-macrophage colony-stimulating factor and interleukin-3 but not with interleukin-5.⁴⁸

The role of macrophages in asthma^{46 49} and rhinitis^{13 50} has been recently highlighted, but there are no available data in sinusitis. In the nasal mucosa of allergic patients, one study has shown no increase in CD68-positive cells,¹³ whereas in another study with EMB11, clone CD68-positive cells were increased during the pollen season or after allergen challenge.⁵⁰ However, EMB11 clone stains dendritic cells and macrophages,⁵¹ whereas the clone used by Bentley et al.¹³ has not been specified. In the present study macrophages studied with the panmacrophage marker CD68 were significantly increased in chronic sinusitis, irrespective of cause. The role of macrophages in chronic sinusitis needs to be further evaluated because these cells have a wide array of secretory activities involved in all phases of inflammatory reaction and healing processes that occur after inflammation.⁵²

Mast cells have a prominent place as primary effector cells of type I allergy, but they are also involved in nonallergic reactions, such as intrinsic asthma, in which mast cells are activated.^{9, 53} In seasonal allergic rhinitis, with the use of conventional staining^{54, 55} or immunohistochemistry,^{13, 56} it has been observed that mast cells are increased during the pollen season. In the present study mast cells are found in the submucosa of patients without sinusitis and in those with sinusitis. The major difference between patients with allergic rhinitis and the two other groups is in the redistribution of mast cells towards the epithelial lumen, which has been shown to be a part of the allergic inflammatory reaction in hay fever.⁵⁶ In our study mast cells did not show a specific pattern of activation, because not only the degranulation score but also mediators released in sinus lavage fluids were not different among the three groups.

T cells are very important in the genesis of allergic disorders.^{8, 57} In this study we examined the whole set of T cells by means of anti-CD3 antibody, and we found 8 times more T cells in patients with allergic rhinitis than in control subjects and patients with nonallergic rhinitis. Nishimoto et al.⁵⁸ found 38% of positive CD3 cells in the maxillary sinus mucosa of 33 patients with chronic sinusitis; however, the allergic status of the patients was not decreased, and there was no control group. In nasal mucosa from patients with allergic rhinitis, CD3-positive cells are greater in number as well.¹³ More immunohistologic data, however, are needed to identify the subsets and cytokine patterns of infiltrating lymphocytes within the sinus mucosa of patients with chronic sinusitis.

Neutrophils were rarely found in the sinus mucosa when hematoxylin and eosin staining or immunohistochemistry was used, and this observation correlates with previous studies.^{10, 59} However, we found many neutrophils in the sinus lavage fluids of both patient groups with marked pattern of activation (MPO release, degranulated aspect when using immunocytochemistry with anti-elastase mAb). This might be due to the inevitable contamination of the sinus lavage fluids by peripheral blood or to bacterial infections. We excluded the diagnosis of active bacterial infections because neutrophils present in the sinus lavage fluids were not pyocytes, the fluids were clear, and results of bacteriologic investigations were negative.

Pathologic examination of the biopsy specimens showed increased numbers of cells in the mucosa of patients with chronic sinusitis. The influx of inflammatory cells may result from recruitment from the blood or clonal expansion of resident cells. We therefore analyzed the cells undergoing DNA synthesis by means of PCNA immunoreactivity. The expression of PCNA in normal tissues correlates well with established parameters of cell proliferation.³⁷ We observed very few PCNA-positive basal epithelial cells in approximately one third of the biopsy specimens from patients with chronic sinusitis with no submucosal staining. Thus as we recently demonstrated in asthma,⁶⁰ the submucosa of sinusitis is not hyperproliferative, suggesting that recruitment from the blood may explain a large part of the inflammatory infiltrate.

Mucosal biopsies and lavage during endoscopic surgery for treatment of chronic sinusitis provide data on the sinus mucosa and show that many cell types are involved. Nonallergic chronic sinusitis resembles nonallergic rhinitis with eosinophilia syndrome because over 90% (23 of 25) of patients have an eosinophilic inflammation, characterized by an increase in ECP in the sinus lavage fluid and/or the presence of eosinophils in the biopsy specimen. However, eosinophils are not the only infiltrating cells because macrophages were present in increased numbers in over 80% (21 of 25).

The term *nonallergic sinusitis with eosinophilic syndrome* is inappropriate because it fails to emphasize the important role of macrophages. This study also provides evidence that chronic sinusitis, which occurs in some patients with allergic rhinitis, can be distinguished on the basis of T cells and intraepithelial mast cells. This finding confirms the individualization of “allergic sinusitis,” often suggested but never demonstrated. However, more studies are needed in patients with chronic sinusitis for three reasons: (1) to determine whether there are different subgroups of patients with nonallergic sinusitis; (2) to determine whether all patients with allergic rhinitis and chronic sinusitis have the same inflammatory patterns or, more probably, whether these characteristics are restricted to some patients only; and (3) to better characterize cell subsets and cytokine patterns of allergic and nonallergic sinusitis. These studies, presently underway in patients with asthma and rhinitis, should enable rapid progress in our understanding of the pathophysiology of sinusitis.

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Maybe *rhinitis*, maybe *sinusitis*, maybe *rhinitis and sinusitis*, but certainly not *rhinosinusitis*!

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Larry Borish

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