

Chronic sinusitis: Risk factors for extensive disease

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Background: Chronic sinus disease is one of the most common diseases in the United States, and little is understood about its pathogenesis.

Objective: To characterize prospectively the immunologic parameters that accompany extensive chronic sinusitis.

Methods: Eighty adult patients with chronic sinus symptoms had a complete blood count with differential, coronal computed tomographic (CT) scan of the sinuses, and serum assays for total IgE, specific IgE, IgA, IgG, IgG subclasses, and pneumococcal titers.

Results: Thirty-seven (46%) patients had extensive sinusitis, defined as a CT score ≥ 12 . A highly significant correlation was noted between the extent of disease and the peripheral eosinophil count ($r = 0.53$, $p < 0.0001$). In keeping with this finding, an eosinophil count $\geq 200/\mu\text{l}$ was strongly associated with extensive disease (odds ratio [OR] = 19.2, 95% confidence interval [CI] = 5.4 to 72.7). Asthma (OR = 6.8, 95% CI = 2.2 to 22.0), atopy (OR = 4.3, 95% CI, 1.5 to 12.8), and age ≥ 50 years (OR = 6.5, 95% CI = 2.0 to 22.2) were also associated with extensive disease. However, the association of eosinophils with extent of disease was independent of asthma, atopy, or age. Levels of IgG1, IgG2, and IgG3 subclasses did not correlate with extent of disease seen on CT scan. Although total IgE and IgG4 levels did correlate with disease, on multiple stepwise regression they did not add to the predictive value of the eosinophil count in identifying patients with extensive disease.

Conclusions: The association of asthma, atopy, eosinophilia, and elevated levels of IgE and IgG4 with extensive disease on CT scan is compatible with the hypothesis that chronic sinusitis may be a disease of immune activation of the T_{H2} type. (J Allergy Clin Immunol 1997;100:185-91.)

Key words: Eosinophils, immunoglobulins, age, asthma, computed tomography

Chronic sinusitis (CS) is a common and often debilitating disease affecting more than 30 million Americans. The morbidity associated with this disorder frequently leads to substantial loss of productivity as well as significant medical expense. It is estimated that more than \$2 billion is spent annually on over-the-counter medica-

Abbreviations used

CI:	Confidence interval
CS:	Chronic sinusitis
CT:	Computed tomography
GM-CSF:	Granulocyte macrophage colony-stimulating factor
OR:	Odds ratio

tions alone for the treatment of CS. Even with aggressive medical and surgical therapy, a significant number of patients continue to have persistent or recurrent disease, leading to frequent courses of antibiotics and multiple surgical revisions. Because increasingly sophisticated antibiotic and surgical therapies have not cured this disease, the identification of parameters that predict which patients have extensive sinus involvement is desirable. The factors associated with an increased risk of extensive sinus disease are pertinent to the investigation of the cause of sinus inflammation, and may ultimately lead to better patient management.

Chronic sinusitis is characterized by inflammatory mucosal thickening and polyp formation in the paranasal sinuses. Histologic studies have demonstrated that the inflammation typically involves the accumulation of activated eosinophils in the sinus mucosa and submucosa.¹ These eosinophils are considered to play a major role in the pathogenesis of CS via the release of their granules, which contain toxic proteins such as eosinophil cationic protein and major basic protein.¹⁻³ Because of the nature of the inflammation and the high prevalence of CS in patients with allergic rhinitis and asthma, allergens are considered to be one of the causes of CS.⁴⁻⁶ Immunodeficiency, particularly IgG subclass and polysaccharide response abnormalities, has also been reported as a cause of CS, mainly in children with recurrent sinopulmonary infections.^{7,8} The mechanism by which an antibody deficiency would predispose to eosinophilic inflammation is unclear.

In our previous report of 47 patients in whom a complete blood count with differential was available, an association was observed between extensive sinus disease on computed tomography (CT) scan and a relative increase in the peripheral eosinophil count.⁹ However, the causality of this relationship has been questioned because of possible confounding factors, namely asthma

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Supported by National Institutes of Health Grants No. AI-01416, No. AI-30840, and No. AI-34607.

Received for publication Sept. 19, 1996; revised March 19, 1997; accepted for publication March 28, 1997.

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0091-6749/97 \$5.00 + 0 1/1/82530

TABLE I. CT scoring system for paranasal sinuses

Based on degree of obstruction				
Nasal passages (1 unit)	0-3 points			
Osteomeatal complex (2 units)	0-3 points			
Based on amount of mucosal thickening	0 points	1 point	2 points	3 points
Frontal (2 units)	0-1 mm	2-5 mm	6-9 mm	≥10 mm
Maxillary (2 units)	0-1 mm	2-5 mm	6-9 mm	≥10 mm
Sphenoid (1 unit)	0-1 mm	2-5 mm	6-9 mm	≥10 mm
Ethmoid (2 units)	0 mm	1 mm	2-3 mm	≥4 mm

The nasal passages and osteomeatal complexes (OMCs) are scored on a scale of 0 to 3 points based on the degree of soft tissue obstruction. The paranasal sinuses were also scored on a scale of 0 to 3 points, but based on the amount of mucosal thickening present as measured in millimeters. The nasal passages and sphenoid sinuses are each considered as being single units, while the OMCs and other sinuses are considered as having two units, a right and a left. The ethmoid sinuses, because of their smaller size, are given higher scores for lesser amounts of mucosal thickening. A CT scan has a maximum of 30 points possible.

and atopy. The present report further examines this association in 80 patients and seeks to clarify the possible role of selective immunoglobulin abnormalities in adults with CS.

METHODS

Patients

Between October 1991 and March 1995, 80 adult subjects with at least a 3-month history of symptoms consistent with chronic sinusitis who were being considered for sinus surgery were recruited from the University of Virginia Otolaryngology and Allergy clinics.¹⁰ The majority of patients were referred for symptoms refractory to traditional therapy, such as antibiotics, decongestants, nasal steroids, and polypectomies. This study was approved by the Human Investigation Committee of the University of Virginia. Patients had both a complete blood count with differential and an extended view coronal CT scan performed during their evaluation. Patients were excluded from the study if they: (1) had received systemic corticosteroids in the 3 weeks before their enrollment, (2) had a previously diagnosed immunodeficiency, or (3) had cystic fibrosis. Only three patients, one with common variable immunodeficiency and two with IgA deficiency, were excluded. A total of 80 patients were included in this study. The clinical features of 47 of these patients were described in our previous report. These 47 patients were chosen out of the 104 patients in that study because they had a CT scan, eosinophil count, and either RAST and quantitative immunoglobulin studies, or the serum had been stocked and was available for those measurements.⁹ Study subjects were 36 men and 44 women with a mean age of 43.1 years (range, 18 to 76 years).

Questionnaire

Each patient was asked to complete a questionnaire regarding the character and duration of the major sinus symptoms, past sinus operations or procedures, recently used medications, and the presence of other illnesses. A symptom score was derived by counting how many of ten common symptoms the patients noted on the questionnaire. Patients were asked specific questions regarding a history of wheezing or asthma, the use of asthma medications, history of chronic lung disease, and smoking habits. A brief allergy history was also obtained that asked about seasonal rhinitis symptoms, prior allergy testing, and the use of allergen immunotherapy. Patients were designated as having asthma if they reported a history of wheezing

and/or a diagnosis of asthma without a significant smoking history or a history of chronic lung disease other than asthma.

CT scan scoring

The patients included in this study had an extended view coronal sinus CT performed as part of an evaluation of their chronic sinus symptoms to determine the need for surgical therapy. Before the scan, patients generally completed 3 weeks of medical therapy consisting of a broad-spectrum oral antibiotic, a nasal steroid, and an oral decongestant. Patients received a topical nasal decongestant at the time of scanning. The CT scans were reviewed by one of the authors (C.D.P.), a neuro-radiologist experienced in the interpretation of sinus CT scans who was blinded to the patient's clinical characteristics. The extent of sinus disease identified by CT scan was quantitated by a previously described scoring system (Table I).⁹

Immunoassays

Serum obtained from patients at enrollment was stored at -20°C until analyzed. Total serum IgE was measured by a fluorometric two-site ELISA by use of the Pharmacia Cap System (Kabi Pharmacia Diagnostics, Uppsala, Sweden). A total IgE ≥100 IU/μl was considered elevated and used as a criterion of atopy.¹¹ Allergen-specific IgE antibody was determined by a previously described quantitative RAST with the use of cyanogen bromide-activated filter paper discs coated with allergen extracts from Hollister-Stier (a Division of Miles Inc., Spokane, Wash.). Allergen extracts used included both dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*), cat epithelium, mixed cockroach, *Alternaria tenuis*, *Aspergillus fumigatus*, short ragweed, and perennial rye grass. After incubation of the extract-coated discs with patient's serum overnight, discs were then washed free of excess serum and radiolabeled goat anti-IgE was used to detect the bound specific IgE antibody. Each assay had a reference control curve established based on *D. farinae*-coated discs incubated in serial twofold dilutions of pooled sera containing 1000 RAST units of IgE antibody to *D. farinae*. Additionally, two positive and two negative control serum samples were run with each assay. Sera containing ≥40 RAST units/μl (a RAST unit being ~0.1 ng of allergen-specific IgE antibody) to an allergen were considered positive.

Quantitative immunoglobulin levels and pneumococcal titers were measured at Nichols Institute (San Juan Capistrano, Calif.). Serum total IgG and IgA were measured by rate

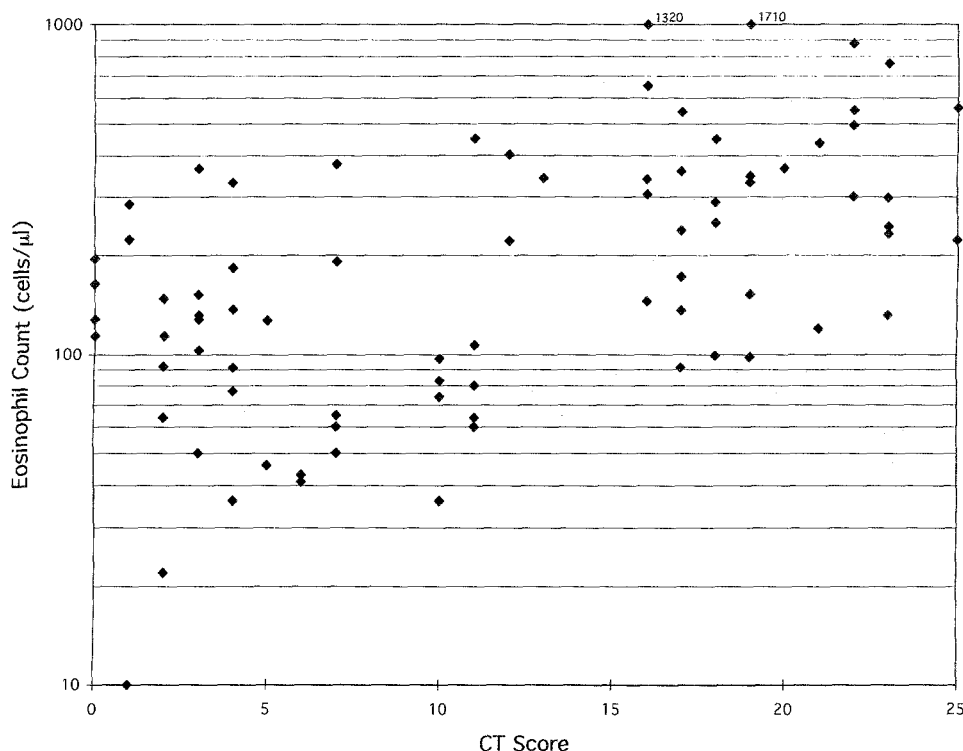


FIG. 1. Correlation of peripheral eosinophil count with sinus CT score. Peripheral eosinophil counts for the 80 patients are plotted on a log scale against their respective sinus CT score ($r = 0.53$, $p < 0.0001$).

nephelometry, with normal adult values ranging from 740 to 1624 mg/dl and from 100 to 498 mg/dl, respectively. Serum IgG subclass levels were determined by colorimetric ELISA with the following normal adult ranges: IgG1, 305 to 1480 mg/dl; IgG2, 35 to 477 mg/dl; IgG3, 10 to 105 mg/dl; IgG4, 4 to 158 mg/dl (with as many as 15% of the normal population having an IgG4 ≤ 4 mg/dl).¹² Levels of specific IgG antibody to the polysaccharide antigens of *Streptococcus pneumoniae* types 3, 8, 12, and 14 were measured by ELISA.¹³ An antibody level <10 absorbance units (AU) is considered to be preimmune.

Peripheral eosinophil count

A complete blood count and differential was performed by automated analysis on blood obtained at enrollment. The absolute eosinophil count was calculated from the total white blood cell count multiplied by the percentage of eosinophils present on the differential.

Statistical analysis

The total IgE, eosinophil count, IgG4, and pneumococcal titers were not normally distributed. Thus, the values were logarithmically transformed before statistical analysis. Nominal variables were analyzed by a chi square test. Linear regression and multiple stepwise linear regression on interval data were performed by use of the SPSS program.

RESULTS

The CT scan scores ranged from 0 to 25 with a mean of 11.4 and a median of 11.1. The scores were not normally distributed; therefore, the patients were grouped into dichotomous variables of extensive disease (CT score ≥ 12) or limited disease (CT score ≤ 12).

Thirty-seven of the 80 patients had extensive disease based on this definition (46%). Twenty-eight patients reported a history consistent with asthma and three fourths of the patients with asthma had extensive disease (OR = 6.8, 95% CI = 2.2 to 22.0). Increasing age was also associated with increasing extent of sinus disease ($R = 0.4$; $p < 0.001$); of the 25 patients who were 50 years of age or older, 76% had extensive disease. No other historical or demographic factors were helpful in predicting extensive sinusitis. Neither the individual symptoms nor the total symptom score predicted the extent of disease seen on CT scan.

The peripheral eosinophil count had the strongest correlation to patient CT scores (Fig. 1). The geometric mean eosinophil count of patients with extensive disease was 309 (95% CI = 245 to 389) versus 91 (95% CI = 68 to 123; $p < 0.0001$). The relationship between the eosinophil count and CT score was examined in two subgroups, patients without asthma or atopy and patients with either asthma, atopy, or the combination of the two. In the 42 patients without asthma or atopy, the presence of an eosinophil count $\geq 200/\mu\text{l}$ was associated with extensive disease, with all but one of these patients having extensive disease (OR = 46.5, 95% CI = 3.6 to 284) (Fig. 2).

Total IgE levels did correlate with extent of disease ($r = 0.35$; $p = 0.02$). Twenty-nine of eighty patients (36%) had a total IgE ≥ 100 IU/ μl and more of these patients had extensive disease (65.5% vs 35.3%, $p <$

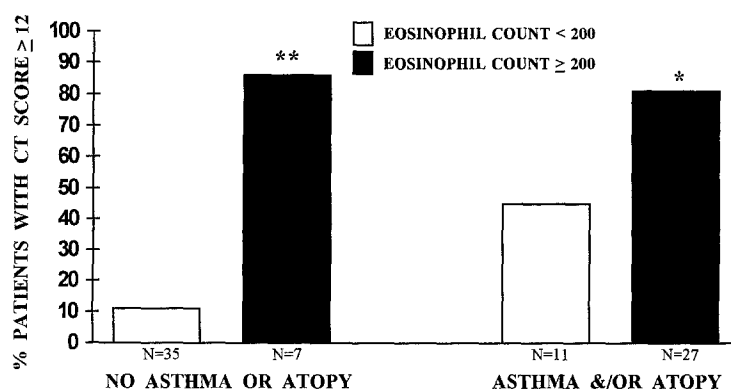


FIG. 2. Effect of asthma and atopy on the relationship of peripheral eosinophil count to extensive sinus disease. The patients were grouped as having asthma and/or atopy or neither disease. Within these two groups, the percentage of patients with an extensive sinus condition is compared for patients with a peripheral eosinophil count of $<200/\mu\text{l}$ and those with a peripheral eosinophil count of $\geq 200/\mu\text{l}$. * $p < 0.05$, ** $p < 0.001$.

TABLE II. Multiple linear regression analysis of the correlation of preoperative parameters and extent of disease on sinus CT scan

	R (individual)	Significance	R (stepwise)	Significance
All patients ($n = 80$)				
Eosinophil count	0.53	<0.001	0.53	<0.001
Age	0.37	<0.001	0.58	<0.001
IgE	0.35	0.002		
IgG4	0.30	0.007		
First surgery only ($n = 63$)				
Eosinophil count	0.53	<0.001	0.53	<0.001
Age	0.43	<0.001	0.62	<0.001
IgG4	0.34	0.01		
IgE	0.30	0.016		

Total IgG, the IgG subclasses, and IgA did not correlate with the extent of disease.

0.02). However, even with a permissive definition of atopy (either having a positive RAST score or having an elevated total IgE level), only 31 of the 80 patients (40%) were atopic. A total of 19 patients had specific IgE antibody level(s) ≥ 40 units/ μl (RAST positive). The positive RAST results included 12 to dust mites, 4 to grass, 4 to cat, 3 to cockroach, 2 to *Aspergillus*, 2 to *Alternaria*, and 2 to ragweed. Compared with patients who had negative RAST results, patients who had one or more positive RAST results did have a greater percentage of extensive disease (73.7% vs 37.7%, $p < 0.01$); moreover, six of the seven patients who were positive for two or more specific IgE antibodies had extensive disease.

No patient was found to be deficient of total IgG or the IgG1 or IgG2 subclasses, nor did the levels of these immunoglobulins correlate with extent of disease. IgG4 positively correlated with extent of disease ($r = 0.34$, $p < 0.01$). Elevated IgG4 was not related to the presence of asthma or atopy, and none of these patients had a previous history of allergen immunotherapy. IgG3 levels did not correlate with extent of disease and only three (3.8%) patients had an IgG3 level lower than the normal range (≤ 10 mg/dl). Two of the three patients had

extensive disease; both of those patients had an eosinophil count $\geq 400/\mu\text{l}$ and an IgG4 level ≥ 40 mg/dl, with one of these patients also having asthma. IgA levels also failed to correlate with extent of disease seen on CT scan. Three patients had IgA levels below the normal range of ≤ 100 mg/dl, but only one was IgA deficient (defined as a serum IgA < 0.15 mg/dl). All three individuals had extensive sinusitis as well as an eosinophil count $\geq 200/\mu\text{l}$, and two of these patients also had an IgG4 level ≥ 40 mg/dl and either asthma or atopy.

Multiple linear regression was performed on age, eosinophil count, and immunoglobulin levels with CT score as the dependent variable. Whereas IgE and IgG4 each individually correlated with the extent of disease on CT scan, they did not add significantly to the correlation between eosinophil count and CT score on stepwise analysis. Regardless of whether patients were presenting for their first or a repeat sinus surgery, age was the only significant contributor to the correlation of eosinophils with the extent of sinus disease (Table II).

Pneumococcal titers were measured in 30 (81%) of patients with a CT score ≥ 12 and 14 (33%) of patients with a CT score < 12 . There was no correlation found between the titers and extent of sinus disease. No

TABLE III. Comparison of risk factors for extensive disease between patients <50 and ≥50 years old

Age (yr)	CT score	No. of patients	% Eosinophil ≥200/μl	% Atopy	% Asthma	Mean IgG3 (mg/dl)	Mean IgG4* (mg/dl)	Mean titer serotype 12* (AU)
<50	<12	37	11%	19%	14%	28.9	12.5	158.1
	≥12	18	61%†	67%‡	61%†	30.9	16.2	118.6
≥50	<12	6	33%	50%	33%	25.5	20.4	54.7
	≥12	19‡	89%§	47%	53%	24.3	26.5	71.3

*Geometric mean used for statistical analysis.

† $p < 0.001$.‡ $p < 0.002$.§ $p < 0.01$.

patients had preimmune levels to serotypes 8 or 12. A preimmune titer to serotype 3 was found in only two patients. Both of these patients had extensive disease, but they were also asthmatic and had an eosinophil count $\geq 200/\mu\text{l}$. Eight patients had a preimmune titer to serotype 14, with only three having extensive sinusitis.

Because of the increase of extensive disease, individuals older than 50 years were analyzed separately as well as part of the group. Compared with the younger patients, older patients had a higher mean eosinophil count (287 vs 122/ μl , $p < 0.0007$), higher mean levels of IgE (101.1 vs 46.2 IU/ μl , $p < 0.05$) and IgG4 (24.8 vs 13.6 mg/dl, $p = 0.006$), but lower mean levels of IgG3 (24.6 vs 29.5 mg/dl, $p < 0.03$) and titers to pneumococcal serotype 12 (66.3 vs 131.7 AU, $p < 0.007$). However, an eosinophil count $\geq 200/\mu\text{l}$ was the only significant predictor of extensive sinus disease in older patients, whereas in younger patients asthma, atopy, and an eosinophil count $\geq 200/\mu\text{l}$ were all highly related to extensive disease (Table III).

DISCUSSION

Among patients who have sinus symptoms refractory to medical therapy, those with a total peripheral eosinophil count $\geq 200/\mu\text{l}$ are likely to have extensive sinusitis. An eosinophil count $\geq 400/\mu\text{l}$ had a positive predictive value of 92%. This association was independent of asthma and atopy and in fact, it was strongest in patients who did not have asthma or atopy. Additionally, an eosinophil count $\geq 200/\mu\text{l}$ was the only factor predictive of extensive sinusitis in patients ≥ 50 years of age. Eosinophil counts of 200 to 600/ μl are considered normal. However, these relatively low eosinophil counts may still indicate immune activation. Hamilos et al.¹⁴ recently demonstrated increased expression of the cytokines IL-3 and granulocyte macrophage colony-stimulating factor (GM-CSF) in the sinus tissues of patients with chronic sinusitis as determined by *in situ* hybridization. These cytokines have been shown to promote eosinophil accumulation and activation as well as prolonged survival in tissues.¹⁵⁻¹⁷ Thus, a plausible explanation for this relative increase in the blood eosinophil count in patients with extensive disease is the release of cytokines, such as IL-3 and GM-CSF, from either T cells in the sinuses or from circulating T cells that were activated in

the sinuses.^{18,19} Acting in an endocrine fashion, these cytokines would promote the growth and differentiation of eosinophil progenitor cells in the bone marrow.²⁰

Although several theories have been postulated as causes of the sinus tissue eosinophilia, the role of allergen sensitization has perhaps generated the greatest debate.⁴ In addition to the increased incidence of atopy reported in patients with CS, the role of allergen sensitization has been supported by studies demonstrating radiographic mucosal thickening and hyperemia of the paranasal sinuses after nasal challenge with a relevant allergen.²¹ On the other hand, Keith et al.²² found no difference in nasal eosinophil cationic protein concentrations related to natural seasonal exposure in patients with nasal polyposis who were allergic to ragweed. They proposed that self-sustaining mechanisms that are largely independent of allergen stimulation were involved. By contrast, a recent study by Hamilos et al.²³ further demonstrated a higher tissue density of T_{H2} -type cytokines, IL-3, IL-4, IL-5, and GM-CSF, in a subset of patients with "allergic" CS as compared with normal controls. While our study also confirms the association of atopy with CS, it appears that the degree of atopy may be as important as its presence, and that it is more pertinent in younger individuals. It is possible that some patients had specific IgE antibodies to allergens not tested; nonetheless, more than 40% of our patients with extensive disease had no evidence of atopy. In the Hamilos et al.²³ study, these "nonallergic" patients were noted to have higher sinus tissue expression of GM-CSF, IL-3, and, surprisingly, IFN- γ . This cytokine pattern could account for the relative eosinophilia found in these patients, but could also implicate other immune mechanisms, such as a form of delayed-type hypersensitivity. Studies showing an increased sinus tissue density of CD8⁺ T cells in patients with CS also support the role of mechanisms other than a T_{H2} -type response.²⁴

Earlier studies involving the use of plain radiography detected significant abnormalities of paranasal sinuses in as many as 31% of patients with asthma, whereas later reports that used CT showed no difference in the extent of sinus disease between patients with and without asthma.^{25,26} The present study found an association between asthma and CS, with 75% of the enrolled patients with asthma having extensive disease. However,

like atopy, this relationship was more important in patients <50 years of age. The increased prevalence of asthma in our study population is consistent with previous reports.^{5, 27} The mechanism(s) responsible for this relationship remains unclear.

Interestingly, IgG4 was the only immunoglobulin subclass that correlated with extent of disease. Unlike previous reports that associated IgG4 deficiency with CS, the extent of sinus disease correlated with higher levels of IgG4, particularly a level ≥ 40 mg/dl. Both IgE and IgG4 are associated with a T_{H2} immune response. However, less than half of the patients with an IgG4 level ≥ 40 mg/dl were atopic, and none of them had received allergen immunotherapy. Although some studies have suggested that IgG4 can trigger mast cell/basophil histamine release, this remains controversial, and most investigators believe elevated levels of IgG4 are a marker of chronic exposure to an antigen rather than a contributor to disease.²⁸ Nonetheless, the association of elevated IgG4 levels with extensive sinusitis, when taken together with the positive relationship of the peripheral eosinophil count and total and specific IgE levels, argues for an ongoing T_{H2} immune response in the pathogenesis of CS. We were unable to substantiate earlier reports that CS is associated with deficiencies of the IgG2 or IgG3 subclasses. In the numerous studies relating a low level of IgG2 to sinusitis, the majority of symptomatic individuals were children who had recurrent infections at multiple sites other than the sinuses and often had other comorbid conditions not seen in our patients.^{3, 29} Nor could we find a significant relationship between IgG3 deficiency and CS.^{8, 30} In a previous study, some of the low IgG3 levels noted normalized over time, suggesting that these may have been an epiphenomenon secondary to an intercurrent infection.³⁰

Our results further illustrate the utility of a CT scoring system in the study of patients with CS. Symptoms or clinical history cannot identify patients with limited or extensive sinus disease on CT scanning. However, the following should be considered as risk factors for extensive sinus disease: age greater than 50 years, a history consistent with asthma, the presence of atopy, an IgG4 level ≥ 40 mg/dl, and a peripheral eosinophil count $\geq 200/\mu\text{l}$. These factors identify a group of patients with evidence of an ongoing inflammatory response, possibly with a T_{H2} phenotype, for whom further investigation may be instrumental in defining the etiology and pathogenesis of inflammation of the sinus mucosa.

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