

Decreased nasal goblet cells in patients reporting topical corticosteroid use

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The nasal epithelium is involved in local inflammatory responses.¹ We have routinely used nasal cytograms as an aid to gauging the degree of nasal mucosal inflammation in patients with allergy. This prospective study relates systematically assessed quantitative changes in nasal mucosal epithelial cells to various clinical characteristics, including disease category, aeroallergy, and treatment modalities in adult patients. Two cell types, namely goblet cells and vacuolated cells, were the focus of this study; and these cells were shown to have significant but separate clinical associations with reported corticosteroid use and IgE levels, respectively.

METHODS

Sixty-eight subjects from the adult allergy clinic were studied over a 12-month period. Clinical data were obtained regarding atopic disease, demographics, comorbid conditions, treatment modalities, and family histories. Nasal mucosal pallor, erythema, edema, and secretions were scored on a scale of 0 to 3. Mucosal scrapings were obtained from the inferior turbinate with a curette-probe (Rhino-probe, Apotex Scientific). These were applied to a glass slide, followed by fixation and staining (Wright-Giemsa stain). Serum IgE concentration and aeroallergen-specific IgE levels (modified RAST) were determined. The smears were then examined by physicians who were blinded to clinical status. Epithelial components of the smears were examined in three well-spread fields. The number of goblet cells and vacuolated cells was divided by the number of epithelial cells to obtain a percentage. Vacuolated cells were identified on the basis of the presence of multiple small intracytoplasmic vacuoles without nucleus displacement to the periphery. Goblet cells had a single large vacuole with a sharply defined interface with the cytoplasm and nuclear displacement to the periphery. Leukocytes were counted in 10 high-power fields, and the percent of eosinophils was calculated. The presence of epithelial cell cilia shedding and degeneration were also noted. Goblet cell clusters (≥ 5 goblet cells together) were counted in the whole slide. A nonallergic reference group of 23 patients from a primary care adult medical clinic was also studied for nasal cytology in the same manner. This reference group had no history of asthma or hay fever, had no current rhinitis symptoms, and had an age distribution similar to that of

the study group. No serologic tests were performed on this group. Statistical analysis was performed by using the JMP package (SAS Institute, Cary, N.C.).

RESULTS

The analysis was performed on 64 allergy clinic patients who had observable epithelial cells. Thirty, five, and twenty-four of these patients had a diagnosis of rhinitis, asthma, or both, respectively. All patients with rhinitis were experiencing symptoms. The current use of nasal corticosteroids (all patients reported use for 1 month or longer) was associated with a significantly lower number and percent of goblet cells (Table I). The number and percent of goblet cells in the reference group was 26 ± 34 and 6.5 ± 8.3 , respectively, and these values did not significantly differ from those observed in patients reporting corticosteroid use. The goblet cell percentages in the reference group were, however, significantly lower than those observed in allergy clinic patients not reporting nasal corticosteroid use (rank sum test, $p = 0.03$). In allergy clinic patients, epithelial cell degeneration was associated with an increased percentage of goblet cells ($9.2\% \pm 7.0\%$) compared with all patients without epithelial cell degeneration ($2.8\% \pm 3.6\%$; t test, $p = 0.0002$). The association between reported nasal corticosteroid use and lower goblet cell percent and number remained ($p < 0.05$) after adjustment for epithelial cell degeneration (analysis of variance).

Goblet cell clusters were more frequently observed in allergy clinic patients reporting no nasal corticosteroid use compared with patients who did (Table I). Adjusting for epithelial cell degeneration in a logistic model did not eliminate the significant association ($p < 0.03$). A greater number of goblet cell clusters was observed in patients reporting no nasal corticosteroid use. The reference group had 2.1 ± 4.0 goblet cell clusters, and this was not significantly different from allergy clinic patients reporting corticosteroid use but showed a trend toward being lower than that observed in allergy clinic patients not reporting corticosteroid use (rank sum test, $p = 0.06$).

For vacuolated cell percentages, the most significant association was with higher IgE levels (>200 IU/ml), where lower percentages were observed ($7.5\% \pm 5.9\%$ vs $13.0\% \pm 9.1\%$; t test, $p = 0.006$). The numbers of vacuolated cells were also lower in patients with elevated IgE levels (27.8 ± 28.9 vs 54.7 ± 47.5 ; t test, $p = 0.008$). The reference group had $12.4\% \pm 1.0\%$ and $45.1 \pm$

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TABLE I. Characteristics of patients reporting and not reporting nasal corticosteroid use

	Patients (with rhinitis) reporting NC use	Patients (with and without rhinitis) not reporting NC use	Patients with rhinitis not reporting NC use
<i>n</i>	18	46	36
Total goblet no.	18.7 ± 17.6	40.8 ± 34.3*	42.4 ± 35.1*
Goblet cells (%)	4.7 ± 4.6	9.7 ± 7.3†	10.1 ± 7.4†
Any goblet cell clusters	5/18	30/46‡	24/37‡
No. of goblet cell clusters	2.0 ± 4.9	4.0 ± 5.7§	4.5 ± 1.5§
Net mucosal appearance score	4.9 ± 2.1	4.0 ± 1.8 (NS)	4.4 ± 6.2 (NS)
IgE level#	362 ± 847	243 ± 431 (NS)	264 ± 455 (NS)
Any RAST ≥ class 2#	7/17	24/46 (NS)	23/37 (NS)
Nasal leukocyte no.	72.3 ± 64.7	55.1 ± 41.9 (NS)	55.6 ± 41.6 (NS)
Nasal eosinophils ≥ 3%	6/18	12/46 (NS)	11/37 (NS)

NC, Nasal corticosteroid; NS, no significant difference from patients reporting NC use ($p > 0.05$).

*Significance of difference from patients reporting NC use, $p \leq 0.005$ (t test).

†Significance of difference from patients reporting NC use, $p \leq 0.001$ (t test).

‡Significance of difference from patients reporting NC use, $p \leq 0.01$ (chi square test).

§Significance of difference from patients reporting NC use, $p \leq 0.05$ (rank sum test).

||Sum of edema, erythema, secretion, and pallor scores.

#RASTs (modified RAST class) were performed for *Dermatophagoides farinae*, American cockroach, short ragweed, timothy/orchard grass, cat epidermis, mouse urine protein, and elm/birch/beech/oak/maple tree, and *Alternaria/Aspergillus/Cladosporium* molds. IgE and RAST were not done in one patient.

36.14 total number of vacuolated cells. These values did not significantly differ from those observed in allergy clinic patients with IgE levels of 200 IU/ml or less but were higher than allergy clinic patients with IgE levels greater than 200 IU/ml (t test, $p = 0.05$). In allergy clinic patients, epithelial cell cilia shedding was associated with higher percentages of vacuolated cells (16.5 ± 8.4 vs 9.9 ± 8.2 ; t test, $p = 0.03$) and higher numbers of vacuolated cells (71.8 ± 49.4 vs 40.1 ± 41.3 ; t test, $p = 0.04$). Adjusting for cilia shedding (analysis of variance) still resulted in a significant association of higher IgE levels ($p < 0.05$) with a lower percent and number of vacuolated cells. There was a significant inverse correlation between the logarithm of total IgE levels and both the percent and absolute numbers of vacuolated cells (Spearman's rho, $p \leq 0.03$).

DISCUSSION

The use of topical corticosteroids is an established treatment in allergic rhinitis, with known effects on mediator release and cellular constitution.^{2,3} The effect on nasal epithelial cells, however, has not been examined. In this study we show a significant difference in the proportion and numbers of goblet cells in patients reporting nasal corticosteroid use. These data bear similarity to a report⁴ of decreased goblet cells in patients with asthma after treatment with topical corticosteroids. The steroid-associated remodeling of airways in asthma described by Laitinen and Laitinen⁴ thus may also be occurring in patients with rhinitis treated with topical corticosteroids.

Vacuolated cells were commonly observed in this study, and their presence has not, to our knowledge, been evaluated or quantitated in allergic rhinitis. In

another study we reported decreases in vacuolated cells in patients with HIV infection reporting chronic nasopharyngeal symptoms.⁵ In this study higher IgE levels (≥ 200 IU/ml) were associated with decreased vacuolated cells. Because elevated IgE levels are one marker of atopic disease, the finding of decreased vacuolated cells may reflect a difference in epithelial cell turnover in certain atopic patients. Taken together, these data suggest that decreased vacuolated cells may be a marker of certain types of nasopharyngeal inflammatory disease. Conceivably, an acceleration of cell degeneration caused by inflammatory stimulation results in a shortened appearance of certain morphologic phases of apoptosis, such as vacuolization.

In summary, we describe alterations in goblet cell and vacuolated cell numbers, which relate to common clinical parameters. Controlled studies are needed to determine whether these relationships are causal in nature.

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