Epithelial Shedding of the Inferior Turbinate in Perennial Allergic and Nonallergic Rhinitis

A Riddle to Solve

Gilead Berger, MD; Joelle Bernheim, MD; Dov Ophir, MD

Objective: To examine the epithelial integrity of the inferior turbinate in patients with perennial allergic rhinitis (PAR) and perennial nonallergic (vasomotor) rhinitis (PNAR).

Design: Nonrandomized, controlled morphometric study.

Setting: University-affiliated hospital.

Patients: Fifty-eight inferior turbinate samples were processed for histological study. Nineteen were from patients with PAR, and 20 were from patients with PNAR. Samples from 19 healthy individuals who underwent rhinoplasty for cosmetic reasons served as control specimens.

Main Outcome Measures: The length of the basement membrane (BM) covered with intact epithelium, covered with a single layer of basal cells, and devoid of epithelium was measured.

Results: Intact respiratory epithelium and areas of partial and complete epithelial denudation were encountered in control specimens and in samples from patients with PAR and PNAR. A significant difference was found between the 3 groups ($P=.001$). The proportion of the BM covered with undamaged epithelium was significantly greater in control specimens and in samples from patients with PNAR than in samples from patients with PAR; the difference between the former 2 groups was non-significant. Most of the epithelial damage in patients with PAR occurred between columnar and basal cells rather than between basal cells and the BM ($P=.02$).

Conclusions: Epithelial shedding of the inferior turbinate is a genuine feature of PAR and is not an artifact of tissue sampling. The finding of greater epithelial exfoliation between basal cells and the more superficial columnar cells than between basal cells and the BM probably reflects different attachment qualities of these cells.

Arch Otolaryngol Head Neck Surg. 2007;133:78-82

THE EPITHELIUM PROVIDES the first line of defense against invading microorganisms and foreign matter. One of the expressions of disrupted mucosal barrier function is epithelial shedding, which is considered part of mucosal remodeling in inflammatory diseases. Support for this long-recognized phenomenon can be found in qualitative observations of postmortem specimens and endobronchial biopsy specimens and in quantitative observations of the sputum and the product of bronchoalveolar lavage of patients with asthma. Epithelial shedding is attributed to the cytotoxic effects of inflammatory mediators such as major basic protein, eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin released from activated eosinophils. Ordóñez et al challenged this commonly accepted view, arguing that epithelial denudation in asthma is not genuine but rather is an artifact of tissue sampling.

Investigators report that epithelial shedding also occurs in the nasal passages of patients with allergic rhinitis. Others not only failed to show a similar response in patients with allergic rhinitis but also questioned its existence. Most of these observations were based on examination of tiny pieces of nasal mucosa using a light microscope or an electron microscope and were qualitative by nature. Among the few studies that performed actual measurements to assess the epithelial integrity of the inferior turbinate (IT) in patients with perennial allergic rhinitis (PAR), the study by Amin et al included patients with perennial nonallergic (vasomotor) rhinitis (PNAR).

The present study provides quantitative and qualitative data about the epithelial integrity of the IT in patients with PAR...
and PNAR and compares these data with those of individuals who had no known history of nasal disease or allergy. Given the controversy surrounding this issue, our objective was to determine whether epithelial shedding of the IT in chronic hypertrophic rhinitis is a fact or an artifact.

METHODS

TISSUE COLLECTION

The material contained 38 samples of the IT. Thirty-nine samples were from patients who had prolonged nasal obstruction originating from marked bilateral IT hypertrophy; otherwise the patients were immunocompetent generally healthy individuals. The patients had failed to respond to medical treatment with antihistamines, decongestants, topical corticosteroids, and mast cell stabilizers given for at least 2 months before the decision was made to operate. Immunotherapy for the patients with a known history of nasal allergy had been ineffective or was refused. None received topical or systemic corticosteroids or had symptoms of upper respiratory tract infection during the month before surgery. Skin prick tests for 20 common airborne allergens were performed at the Allergy and Clinical Immunology Unit, Meir Medical Center, to differentiate between patients with and without allergy. Nineteen of 39 patients were allergic to house dust mite and were defined as having PAR. The remaining 20 patients had a negative response to the allergens and were defined as having PNAR. All patients underwent inferior turbinectomy that included removal of the bone and the surrounding mucosa. Nineteen individuals who had rhinoplasty for cosmetic reasons served as a control group. On examination, their IT appeared normal, and they had no symptoms or signs of nasal or other debilitating disease. Skin prick test results for 20 common airborne allergens were negative. To facilitate postoperative nasal breathing, the anterior third of the patients’ IT was excised during surgery. The three groups were age matched (P = .15). The study protocol was approved by the institutional review board of the Meir Medical Center, Kfar Saba. Known benefits, risks, complications, and alternatives to surgery were discussed preoperatively, and all patients signed an informed consent form before enrollment.

TISSUE PREPARATION

All samples underwent histological and immunohistochemical processing at the Ear, Nose, and Throat Histopathologic Research Laboratory of the Department of Otolaryngology–Head and Neck Surgery, Meir Medical Center. They were fixed in 10% buffered formaldehyde; thereafter, the IT bone was separated by sharp dissection. The samples were then dehydrated with increasing concentrations of alcohol and were embedded in paraffin blocks. Serial 5-μm-thick tissue sections were cut at a plane perpendicular to the mucosal surface and were attached to slides coated with poly-1-lysine (Sigma-Diagnostics Inc, St Louis, Mo). Representative sections of the pathologic and normal ITs were stained with hematoxylin-eosin. The epithelium on mucosal surfaces, which is delicate and can easily break, was handled carefully to ensure the integrity of the samples at the time of retrieval and preparation.

MORPHOMETRIC MEASUREMENTS

The samples were coded at random and were analyzed blindly using an eyepiece of the microscope containing a 10×10-square reticule. The length of the reticule at magnification ×100 was 0.8 mm. For accurate comparison, a section was selected from each sample, positioned at the same distance along the course of the anterior third of the IT and comprising the medial, inferior, and lateral surfaces. Similar to the example of Ordoñez et al,6 the length of the basement membrane (BM) (1) covered with intact pseudostratified ciliated columnar epithelium, (2) covered with a single layer of basal cells, and (3) devoid of epithelial cells was measured. The total length of the BM was determined by adding the lengths of the corresponding areas of each of the 3 measurements. The numerator for calculating the percentage (ie, the relative proportion) of the BM covered by each of these lengths was the sum of length of the corresponding areas, and the denominator was the total length of the BM.

Ethical reasons limit our ability to study all portions of the IT in healthy individuals; therefore, quantitative assessment was carried out for the anterior third of the IT in the controls. Quantitative assessment of the middle and posterior portions of the IT was performed only for patients with PAR and PNAR.

STATISTICAL ANALYSIS

The proportions were transformed to the arcsine square root scale to reduce differences in variance across groups and to improve the adequacy of the normal approximation. Analysis of variance using the Tukey method for multiple comparisons was performed to determine the epithelial integrity of the IT in patients with PAR and PNAR and in controls. Analysis of variance was also used for comparing epithelial length and age differences. The proportion of partial and complete epithelial denudation within each of the 3 groups was determined using the paired t test. Measurements were expressed as mean±SD. Significance was set at P<.05.

RESULTS

Except for intact areas, the following 2 forms of epithelial damage were encountered: (1) partial denudation of epithelial cells (ie, the BM was covered with a single layer of basal cells without ciliated cells or goblet cells) and (2) complete denudation of epithelial cells, including basal cells. Both forms were observed in controls and in patients with PAR and PNAR but in varying proportions as noted herein (Figure 1).
As summarized in the Table, the mean lengths of the IT BM in patients with PAR and PNAR and in controls were similar (13.0 ± 5.2, 10.9 ± 4.4, and 10.4 ± 4.7 mm, respectively; *P* = .20). The Table also lists the relative proportions of intact partially denuded (ie, with a single layer of basal cells) and completely denuded BMs in patients with PAR and PNAR and in controls. Assessment of the epithelial integrity demonstrated a significant difference between the 3 groups (*P* < .001). Further analysis showed a significant difference between the relative proportions of the BM covered with undamaged epithelium in patients with PAR compared with those of controls and patients with PNAR. The difference between the latter 2 groups was insignificant. This indicates significantly greater epithelial damage in patients with PAR than in controls or in patients with PNAR. For the type of epithelial damage, a significantly greater percentage of the BM was covered with a single layer of basal cells compared with completely denuded areas in controls and patients with PAR (*P* = .009 and *P* = .02, respectively), whereas in patients with PNAR the difference did not reach statistical significance (*P* = .12). These findings attest to greater epithelial damage occurring between the basal cells and the more superficially columnar ciliated and goblet cells rather than between the BM and the epithelial basal cells.

**Table. Epithelial Length and Relative Proportion of Intact, Partially Denuded, and Completely Denuded Basement Membrane in Patients With PAR and PNAR and in Control Subjects**

<table>
<thead>
<tr>
<th>Group</th>
<th>Epithelial Length, mm†</th>
<th>Intact Epithelium</th>
<th>Partially Denuded Epithelium</th>
<th>Completely Denuded Epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAR</td>
<td>13.0 ± 5.2</td>
<td>42.7 ± 19.2</td>
<td>35.7 ± 14.6</td>
<td>21.7 ± 17.7</td>
</tr>
<tr>
<td>PNAR</td>
<td>10.9 ± 4.4</td>
<td>57.9 ± 22.6</td>
<td>26.3 ± 18.1</td>
<td>16.0 ± 11.2</td>
</tr>
<tr>
<td>Control</td>
<td>10.4 ± 4.7</td>
<td>72.1 ± 12.5</td>
<td>18.6 ± 10.0</td>
<td>9.2 ± 9.0</td>
</tr>
</tbody>
</table>

Abbreviations: PAR, perennial allergic rhinitis; PNAR, perennial nonallergic (vasomotor) rhinitis.

*Data are given as mean ± SD.
†As measured from the sections of the anterior one third of the inferior turbinate.

**Figure 2.** A section of the inferior turbinate from a patient with perennial allergic rhinitis showing a thin pinkish layer of plasma-derived gel (arrow) over the denuded basement membrane (hematoxylin-eosin, original magnification ×400).

### QUALITATIVE ASSESSMENT

Qualitative assessment carried out for the middle and posterior portions of the IT in patients with PAR and PNAR showed the 3 stages of epithelial formation with marked partial and complete epithelial denudation. Examination of the completely denuded areas using high-power magnification revealed a thin pinkish layer of plasma-derived gel over the denuded BM (Figure 2) in some part of the samples from patients with PAR, probably reflecting the early stages of epithelial restitution.

There is debate as to whether and to what extent epithelial shedding occurs in allergic rhinitis. We found that the extent of epithelial shedding was significantly greater in patients with PAR compared with controls and patients with PNAR. This supports the hypothesis that allergic rhinitis is associated with increased epithelial damage and exfoliation of the IT. The inclusion of an appreciable number of samples for each of the 3 groups and the finding of epithelial shedding in healthy and inflammatory airways reduce the possibility of error and affirm the conclusion that the phenomenon is genuine and is not an artifact of tissue sampling.

To the best of our knowledge, only 3 other studies have performed actual measurements to assess the epithelial integrity of the IT. One study agrees with our findings, and 2 studies failed to show significant differences between patients with PAR and a control group. We suspect that the disparity between the studies is attributable to differences in patient selection or in methods of investigation. Our study showed that epithelial shedding prevails in patients who had a relatively severe clinical course of nasal obstruction that was treated surgically after failed attempts with antihistamines, decongestants, topical corticosteroids, and mast cell stabilizers. Likewise, Amin et al provide laboratory evidence that epithelial shedding occurs in more severe cases of PAR, with greater sensitivity to pollens during the pollen season than out of season. The authors also observed a higher number of eosinophils in areas of epithelial exfoliation. Chanez et al did not find epithelial shedding in patients with asthma and PAR, who (according to their symptoms and endoscopic scores) had only mild to moderate severity of nasal disease. Contrary to our methods of investigation using representative sec-


Downloaded From: by a Non-Human Traffic (NHT) User on 11/24/2018
tions of the medial, inferior, and lateral aspects of the an-
terior portion of the IT, both of the other studies13,14 used
tiny biopsy specimens from the anterior end of the in-
terior aspect of the IT or from unspecified sites. Further in-
vestigations are warranted to examine whether epithelial
damage occurs throughout the entire IT or whether it is
confined to specific regions, as well as to assess the extent
of the damage and whether it is homogeneously distrib-
uted along the various regions of the IT.

Although different in origin, PNAR shares common
characteristics with PAR regarding mast cell and goblet
cell populations.16,17 As mentioned earlier, patients with
PNAR had an extent of epithelial shedding similar to that
of controls but significantly less pronounced than that in
patients with allergy. Others report the phenomenon
in detail and found that (similar to patients with PAR out-
side of the pollen season) the BM of patients with PNAR
displayed a significantly greater extent of epithelial denu-
dation compared with controls but showed a lesser ex-
tent of denudation compared with patients with PAR dur-
ing the pollen season.10

Partial epithelial denudation of the IT, which is char-
acterized by a selective loss of columnar cells that leaves
a single layer of basal cells to cover the BM, was signifi-
cantly more abundant than complete denudation (ie, complete stripping of cellular coverage) in our patients
with PAR. A similar pattern of epithelial exfoliation pre-
vails in the lower airways of patients with asthma.16 In
both locations, most epithelial disruption occurs in the
“superficial plane” between the basal and columnar cells
rather than in the “deep plane” between the BM and epi-
thelial basal cells. This may be explained by differences
in anchoring characteristics of columnar and basal cells.
It seems that the anchoring of the columnar cells to
basal cells through desmosomal connections19 is less
resistant and is easily disrupted compared with the
anchoring of the basal cells to the lamina densa of the
BM, where the attachment is through hemidesmosomal
connections and other adhesive mechanisms involving
integrins and anchoring filaments.20

Bronchial epithelial disruption of patients with
asthma is traditionally related to cytotoxic effects of
eosinophil granule proteins. A similar mechanism was
shown in the paranasal epithelium of patients with
chronic sinusitis.21 The following 2 other mechanisms
inducing epithelial damage were suggested: (1) plasma
exudate leaking through vascular epithelial gaps and (2)
disturbances in cell-to-cell adhesion.13 Regarding
disturbances in cell-to-cell adhesion, the authors
showed that higher expression of the anti-adhesion
molecule episialin, which inhibited integrin-mediated
cell adhesion to extracellular matrix components and
caus ed marked reduction in cell adhesiveness, was
found in the bronchial epithelium of patients with
asthma. Given that the mechanism underlying epithe-
lial shedding in the IT of patients with PAR is not fully
understood, further study is needed to establish
whether these mechanisms or others apply.

Experimental tracheal deep epithelialization induced rapid
formation of a protective extravasated plasma layer
over the BM minutes after denudation, followed by
epithelial cell dedifferentiation and migration to fill
the gap.22 In our study, we observed a thin pinkish gel
layer over the denuded BM in patients with PAR. The
gel is suggested to be of plasma-derived factors and
probably reflects an early phase of epithelial restitution.22 This finding further supports our conclusion
that epithelial shedding is a genuine pathologic expression of disrupted mucosal barrier function in patients with PAR.

CONCLUSIONS

The present study demonstrates a significantly greater pro-
portion of epithelial shedding in patients with PAR com-
pared with controls and patients with PNAR, suggest-
ning that the phenomenon is a genuine feature and is not
an artifact of tissue sampling. The greater epithelial dam-
age found between basal cells and the more superficial
columnar cells than between basal cells and the BM prob-
ably reflects the existence of different attachment quali-
ties of these cells.

Submitted for Publication: June 26, 2006; accepted Au-
 gust 26, 2006.

Correspondence: Gilead Berger, MD, Ear, Nose, and
Throat Histopathologic Research Laboratory, Depart-
ment of Otolaryngology—Head and Neck Surgery, Meir
Medical Center, Kfar Saba 44281, Israel (bergerg45
@netvision.net.il).

Author Contributions: Drs Berger and Ophir had full
access to all the data in the study and take responsi-
bility for the integrity of the data and the accuracy of
the data analysis. Study concept and design: Berger. Acquisi-
tion of data: Berger. Analysis and interpretation of data:
Berger, Bernheim, and Ophir. Drafting of the manuscript:
Berger. Critical revision of the manuscript for important
intellectual content: Berger, Bernheim, and Ophir.
Obtained funding: Ophir. Administrative, technical, and
material support: Berger. Study supervision: Berger,
Bernheim, and Ophir.

Financial Disclosure: None reported.

Acknowledgment: We thank Ilana Gelernter, MA, for sta-
tistical consultation and Rachel Berger for writing and
editing assistance.

REFERENCES

1. Houston JC, De Navasquez S, Trounce JR. A clinical and pathological study of
fatal cases of status asthmaticus. Thorax. 1953;8:207-213.
2. Laitinen LA, Heino M, Laitinen A, Kava T, Hahtela T. Damage of the airway epi-
3. Naylor B. The shedding of the mucusa of the bronchial tree in asthma. Thorax.
cells in bronchoalveolar lavage in subjects with mild asthma: relationship to bron-
5. Gleich GJ, Flavahan NA, Fujisawa T, Vanhoutte PM. The eosinophil as a media-
tor of damage to respiratory epithelium: a model for bronchial hyperreactivity.
in asthma: artifact or pathology? Am J Respir Crit Care Med. 2000;162:2324-
2329.
7. Watanabe K, Watanabe I. Changes of nasal epithelial cells and mucus layer after


