Association of Asthma With Clinically Aggressive Recurrent Respiratory Papillomatosis

Philip K. Robb Jr, BA; Paul M. Weinberger, MD; Helen Perakis, MD; Anya Li, MD; Adam M. Klein, MD; Michael M. Johns III, MD; Lacey K. Adkins, BS; Gregory N. Postma, MD

Objective: To determine whether there is an association between the presence of asthma and a clinically aggressive disease course in patients with recurrent respiratory papillomatosis (RRP).

Design: Retrospective multi-institutional cohort study (level III evidence).

Setting: Two academic medical centers in the southeastern United States.

Patients: Adult patients with RRP treated at the Georgia Health Sciences University or at the Emory University School of Medicine between January 1998 and December 2009. Excluded from the study were adult patients who had been diagnosed as having RRP when they were a child (<18 years).

Main Outcome Measures: The primary outcome measure was the presence of a clinically aggressive RRP disease course (defined as distal spread of disease, >4 procedures performed in 12 months, or progression to laryngeal squamous cell carcinoma). The secondary outcome measure was the frequency of required surgical interventions.

Results: Identified were 90 patients with RRP (age range at first diagnosis, 19.1-86.4 years). Seventeen patients had aggressive disease, and 73 patients had nonaggressive disease. Seven patients had a history of asthma, 5 of whom were using daily inhaled corticosteroids. An association was noted between the presence of asthma and aggressive RRP, which was found in 57% (4 of 7) of patients with asthma vs 16% (13 of 83) of patients without asthma (P = .02). Patients with asthma using daily inhaled corticosteroids were especially likely to have aggressive RRP, which was found in 80% (4 of 5) of corticosteroid users vs 15% (13 of 85) of nonusers (P = .004).

Conclusions: Patients with asthma, particularly those using daily inhaled corticosteroids, may have a more clinically aggressive RRP course. The cause of this association is unclear, and clinical recommendations should not yet be made based on these data.


Recurrent respiratory papillomatosis (RRP) is a disease associated with human papillomavirus (HPV) type 6 (HPV-6) and HPV-11 and is characterized by hyperplastic epithelial proliferation affecting the upper respiratory tract. Recurrent respiratory papillomatosis has a bimodal age distribution, peaking in children younger than 5 years and again between the ages of 20 and 30 years. The initial symptom in pediatric and adult patients is typically dysphonia and if left untreated will often progress to stridor or impending respiratory distress in more advanced disease. The most common sites affected are the glottis and supraglottis, but it can spread to the subglottis, trachea, and distal aerodigestive tract in approximately 5% of patients. Malignant transformation to squamous cell carcinoma has been associated with RRP, although this is uncommon.

Recurrence is characteristic of RRP, with some patients requiring more than 100 surgical procedures over their lifetime. This represents an enormous financial burden for patients, physicians and health care providers, and society, with total health care costs often exceeding $400 000 per patient. Current therapy for RRP is surgical intervention, with primary goals of adequate airway maintenance and restoration of a serviceable voice. Accepted methods of surgical treatment include microlaryngeal surgery using “cold steel” instruments, microdebriders, and lasers (with general anesthesia or as an office-based procedure without sedation). Antiviral medications have been proposed (such as cidofovir or interferon), as well as other adjuvant thera-
ies (including indole-3-carbinol, ribavirin, mumps vaccine, and photodynamic therapy). No treatment has been successfully evaluated by a controlled clinical trial to our knowledge, so there remains considerable uncertainty about the "best" treatment.

The clinical course of RRP is widely variable, with some patients requiring frequent surgical intervention, while others experience a benign disease course. Pediatric patients with RRP typically require more frequent surgical interventions and have a more aggressive disease course, as do patients having HPV-11 (compared with patients having HPV-6). No other factors to date have been identified as predictors of aggressive RRP.

Increased epithelial proliferation and progression of several disease processes, including cancer, have been linked to chronic inflammation. In particular, cervical cancer caused by HPV may have a relationship with chronic inflammation in the progression to invasive cancer. Asthma is a chronic inflammatory condition primarily affecting the epithelium and associated tissues of the respiratory system. In this study, we hypothesized that the presence of asthma may be associated with a clinically aggressive disease course in patients with RRP.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Nonaggressive RRP (n = 73)</th>
<th>Aggressive RRP (n = 17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first diagnosis, mean (95% CI), y</td>
<td>90</td>
<td>47.6 (43.9-51.2)</td>
<td>47.8 (41.0-55.6)</td>
<td>.96</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58</td>
<td>44</td>
<td>14</td>
<td>.10</td>
</tr>
<tr>
<td>Female</td>
<td>32</td>
<td>29</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Self-reported medical history of asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>.02</td>
</tr>
<tr>
<td>No</td>
<td>83</td>
<td>70</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Use of daily inhaled corticosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>.004</td>
</tr>
<tr>
<td>No</td>
<td>85</td>
<td>72</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RRP, recurrent respiratory papillomatosis.

^a Age range, 19.1 to 86.4 years.

METHODS

Institutional review board approval was granted for this study (Georgia Health Sciences University [GHSU] HAC06-01-177 and Emory University School of Medicine [hereafter Emory] IRB00018986). The design was a retrospective multi-institutional cohort study (level III evidence). Medical records from the Department of Otolaryngology and Center for Voice and Swallowing Disorders at GHSU and from the Emory Voice Center were reviewed. Adult patients (>18 years) treated for RRP of the upper aerodigestive tract between January 1998 and December 2008 (at GHSU) or between January 1998 and December 2009 (at Emory) were identified. Pediatric patients were specifically excluded from this analysis. We chose to limit this study to adult patients with RRP, as there are several differences between adult-onset and pediatric-onset RRP. These include variation in overall disease aggressiveness, potential differences in RRP association with inflammation, and possible confounding by the general misclassification of pediatric airway conditions as asthma.

Recorded were clinical and pathologic data, including gender, age at disease presentation, self-reported use of inhaled corticosteroids, and the presence of comorbidities (including asthma) by medical history. Confirmatory objective testing of asthma (eg, by pulmonary function testing) was not performed. All surgical procedures were recorded, such as unscheduled office-based procedures using angiolytic pulsed-dye laser or potassium-titanyl-phosphate laser and procedures using general anesthesia, including microdebridement and carbon dioxide laser treatment. The maximum number of procedures performed per consecutive 12-month period was recorded. Patients were divided into 2 subgroups having clinically aggressive vs nonaggressive disease. Aggressive disease was defined as the occurrence of any of the following: distal spread of disease, more than 4 procedures performed in 12 months, or progression to laryngeal squamous cell carcinoma.

The primary outcome measure was the presence of a clinically aggressive RRP disease course. The secondary outcome measure was the frequency of required surgical interventions. Associations among gender, the presence of asthma, daily inhaled corticosteroid use, and a clinically aggressive RRP disease course were compared by contingency table analysis using Fisher exact test for statistical significance. Comparison of the number of procedures performed relative to the presence of asthma was by Wilcoxon rank sum test. Ages in patients with clinically aggressive vs nonaggressive RRP were compared by t test. All comparisons were 2-tailed and were performed using commercially available statistical software (SPSS 14.0 for Windows; SPSS Inc, Chicago, Illinois). P < .05 was considered statistically significant.

RESULTS

DEMOGRAPHICS

Identified were 90 adult patients with RRP (38 treated at GHSU and 52 treated at Emory). Their ages ranged from 19.1 to 86.4 years (mean age, 47.6 years), and 32 were female and 58 male. Demographic data for the cohort are summarized in the Table.

CLINICALLY AGGRESSIVE VS NONAGGRESSIVE RRP

The maximum number of surgical procedures performed per patient in 1 year (any consecutive 12-month period) ranged from 1 to 11 (median, 2). Fifteen patients required more than 4 procedures per year. Two pa-
patients (both requiring >4 procedures per year) had distal spread of disease. An additional 2 patients developed laryngeal squamous cell carcinoma. Cases were divided into clinically aggressive vs nonaggressive disease. Using our definition, 17 patients had clinically aggressive disease, and 73 patients had nonaggressive disease.

COMORBIDITIES AND CORRELATIONS

A trend was noted for an association between gender and a clinically aggressive RRP disease course, with 9% (3 of 32) of female patients compared with 24% (14 of 58) of male patients having aggressive disease, although this was not significant (P = .10, Fisher exact test). Seven patients had a history of asthma (based on self-reported medical history), and 5 patients were using daily inhaled corticosteroids. No patients without asthma were using inhaled corticosteroids. There was an association between the presence of asthma and a clinically aggressive RRP disease course, with 24% (4 of 17) of patients with clinically aggressive RRP vs 4% (3 of 73) of patients with nonaggressive RRP having asthma (P = .02, Fisher exact test). Patients having RRP with asthma required more procedures per 12-month period than patients having RRP without asthma (median [interquartile range], 3 [6] vs 2 [2] procedures per year), although this was not significant at P = .18 (Wilcoxon rank sum test). These associations were more striking when only patients who were using daily inhaled corticosteroids (for asthma treatment) were considered. Among these, 4 of 5 patients (80%) had clinically aggressive RRP, while 13 of 85 patients (15%) not receiving corticosteroids had aggressive RRP (P = .004, Fisher exact test). Patients with RRP using daily inhaled corticosteroids required a median (interquartile range) of 5 (5) procedures per year compared with a median (interquartile range) of 2 (2) procedures per year in those not using daily inhaled corticosteroids (P = .04, Wilcoxon rank sum test). These data are summarized in the Figure.

The clinical manifestations of RRP can vary widely, with some patients experiencing an indolent disease course and others requiring frequent surgical debridements. Several attempts have been made to distinguish aggressive from nonaggressive RRP. A widely used measure is the score by Derkay et al,13 in which airway subsites are individually scored for RRP disease extent to yield a composite score. Anatomic scores exceeding 20 are considered to represent high risk for aggressive RRP requiring frequent surgical debridement.13 Potential criticisms of the scoring system by Derkay et al include the somewhat cumbersome nature of individually scoring multiple different anatomical subsites, making this scoring system less applicable to retrospective studies. Another method of defining aggressive RRP used the total number of surgical procedures (with >40 lifetime operations representing aggressive RRP).6,13 Using this method, patients with recent disease onset or follow-up for unequal periods compared with others in a cohort are likely to be misclassified. A third definition is based on the number of procedures per year. Doyle et al12 proposed 3 or more procedures per year, more than 10 lifetime procedures, or distal spread of disease as defining characteristics for aggressive RRP. Our patient population was treated not only with surgical debridement using general anesthesia but also with office-based treatment using photoangiolytic laser therapy.16-18 The photoangiolytic laser is an emerging treatment modality for RRP and was not widely available at the time of the study by Doyle et al. The availability of unsedated office-based treatment may result in more frequent treatment because some of the inconvenience and risks of procedures that require general anesthesia have been eliminated.5,18 In the present study, we elected to base our definition of aggressive disease on that by Doyle et al (using the maximum number of procedures per 12-month period or distal

Figure. Correlation between the presence of asthma by self-reported medical history and a clinically aggressive recurrent respiratory papillomatosis (RRP) disease course. A, Patients with asthma were more likely to have a clinically aggressive RRP disease course compared with patients without asthma (P = .02). B, This association was more pronounced when comparing patients with asthma using vs not using daily inhaled corticosteroids (P = .004).
spread of disease to denote aggression) but chose a cutoff of 4 surgical procedures per year (instead of ≥3 per year). We also included progression to laryngeal squamous cell carcinoma as a potential defining characteristic of aggressive RRP, as suggested by some groups.3,10

We found a strong epidemiologic link between asthma (and, strikingly, patients with asthma using daily inhaled corticosteroids) and a clinically aggressive RRP disease course. Because our study was retrospective in nature, it is impossible to draw conclusions regarding causes. We propose 3 possibilities that may explain this association and will discuss each briefly. The first possibility is that asthma represents a perturbation of the immune system. This chronic inflammatory process affects not only bronchial but also laryngeal epithelium, leading to more rapid epithelial growth and clinically aggressive disease. A second possibility is that inhaled corticosteroids (standard second-line therapy for asthma) may directly produce local immunosuppression within the laryngeal epithelium, reducing immune system surveillance and allowing virally influenced RRP to progress. A third possibility is that inhaled corticosteroids may directly cause upregulation of low-risk viral gene transcription, leading to decreased host cell cycle control and increased cell proliferation. Investigations in our laboratory are being planned to test each of these hypotheses.

Relative to the first hypothesis, evidence for an association between chronic inflammation and several diseases is emerging, including cervical cancer caused by HPV. Asthma is a chronic inflammatory disease affecting the airway epithelium, characterized by perturbation of the immune system toward a helper T-cell subtype 2 (Th2) response. Some of these alterations include increased secretion of proinflammatory cytokines and chemokines, including eotaxin, interleukin 4, and RANTES (regulated on activation, normal T cell expressed and secreted).19 Both asthma and RRP may be disease states characterized by immune system bias toward a Th2 response.20 Patients with more severe asthma (and thus requiring inhaled corticosteroids) may also have more aggressive RRP disease by virtue of a similar underlying perturbation of the immune system.

The second potential explanation for the link between asthma and aggressive RRP is that inhaled corticosteroids may produce a local immunosuppressive effect on the laryngeal epithelium.21 These agents are standard second-line therapy for asthma, and 71% (5 or 7) of our patients with asthma were receiving inhaled corticosteroid therapy. Although inhaled corticosteroids are designed to be deposited on the epithelium of the bronchioles, some drug is also deposited to a lesser degree on the laryngeal epithelium.22 The only evidence to date supporting this possibility is this single case report by Fairfax et al22; therefore, further research in this area is needed. Local tissue effects of inhaled corticosteroids on normal laryngeal epithelium can include atrophy of the laryngeal mucosa, laryngeal inflammation and edema, and vocal fold atrophy.23 There have been no specific studies of laryngeal epithelial–specific immune system changes due to inhaled (or other) corticosteroids. It can be surmised from investigations of bronchoalveolar changes that these changes would likely include suppression of pro-inflammatory cytokine production, blockade of local T-cell recruitment, and induction of immunosuppressive T-regulatory and interleukin 10–secreting T cells.24 Epithelial cells infected with HPV may be under constant immune surveillance and elimination. Local immunosuppression would then allow increased growth and proliferation of infected cells, possibly leading to a clinically more aggressive disease course. This hypothesis should be tempered by the fact that no epidemiological studies have yet demonstrated an association between systemic immunosuppression and RRP.

The third possibility is that inhaled corticosteroids may directly cause upregulation of low-risk viral gene transcription, leading to decreased host cell cycle control and increased cell proliferation. The upstream regulatory region serves as a promoter site for HPV early genes.25 The protein products of these early genes, including HPV E6 and E7, are responsible for inducing host (human epithelial) cell cycle dysregulation and inhibition of apoptosis through their actions on cellular p53 and Rb proteins.26 Most important, glucocorticoid response elements have been demonstrated within the upstream regulatory region of several high-risk HPV types.26 Bromberg-White et al27 found that binding of glucocorticoids resulted in upregulation of viral E6 and E7 transcription, resulting in loss of cell cycle control and apoptosis resistance in high-risk HPV-31. Therefore, glucocorticoids could conceivably cause worsening of HPV-mediated cell cycle dysregulation, resulting in increased infected epithelial cell proliferation (and potentially more clinically aggressive disease). To date, no studies have been performed to determine whether the upstream regulatory region of low-risk HPV types (eg, HPV-6 or HPV-11) contains glucocorticoid response elements.

It is likely that these 3 possible explanations are not mutually exclusive. As well, there may be other possible explanations for the association between the presence of asthma and a clinically aggressive RRP disease course.

Limitations of our study include the retrospective nature of the review and the small cohort size for patients with RRP and asthma. The presence of asthma and inhaled corticosteroid use were self-reported, and no objective measurement of asthma (such as pulmonary function testing) was performed. In addition, information on duration and dosage intensity of the inhaled corticosteroids was unavailable for these patients. Our initial findings from only 40 patients are herein corroborated across 2 separate institutions, lending a certain amount of validity to our results.28 Efforts are in progress to expand our study to objectively evaluate patients with RRP for the presence of asthma and to include patients at other institutions.

In conclusion, our finding that patients with asthma may have more clinically aggressive RRP is the first such documentation in the literature to date. The exact cause of this association is unclear. This is a preliminary correlative study with a small cohort size, and further data are needed before clinical recommendations can be made or inferred.

Submitted for Publication: May 21, 2010; final revision received December 3, 2010; accepted December 7, 2010.
Correspondence: Gregory N. Postma, MD, Department of Otolaryngology and Center for Voice and Swallowing Disorders, Georgia Health Sciences University, 1120 15th St, Room BT4633, Augusta, GA 30912 (gpostma@georgiahealth.edu).

Author Contributions: Mr Robb and Drs Weinberger, Johns, and Postma had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Mr Robb and Dr Weinberger contributed equally to this work. Study concept and design: Robb, Weinberger, Perakis, Klein, and Postma. Acquisition of data: Robb, Perakis, Li, Klein, Johns, Adkins, and Postma. Analysis and interpretation of data: Robb, Weinberger, Johns, and Postma. Drafting of the manuscript: Robb, Weinberger, and Perakis. Critical revision of the manuscript for important intellectual content: Weinberger, Li, Klein, Johns, Adkins, and Postma. Statistical analysis: Weinberger. Administrative, technical, and material support: Robb, Perakis, Li, Johns, and Adkins. Study supervision: Postma.

Financial Disclosure: None reported.

Previous Presentation: Portions of this work were presented at the Combined Southern & Middle Sections Program of the Triological Society; January 9, 2009; Bonita Springs, Florida.

Additional Contributions: Lisa Barnhill, BA, and Anthony Anfuso, MD, provided administrative research support services. Li Fang Zhang, PhD, gave statistical advice, and Martin Birchall, MB, MA(Hon), MD(Cantab), FRCS, FRCS (ORL) assisted with manuscript revision.

REFERENCES

26. Weinberger PM, Robb PK Jr, Carlson HT, Perakis H, McChesney JP, Postma GN. Predictors of clinically aggressive recurrent respiratory papillomatosis. Presented as a poster at the combined Annual Meeting of the Southern and Middle Sections of the Triological Society; January 9, 2009; Bonita Springs, Florida.