Introduction

Recurrent respiratory papillomatosis (RRP) is a disorder of the respiratory epithelium seen in fewer than ten people per 100,000 per year. It has a bimodal distribution, with the first peak occurring in children younger than five years of age and the second peak occurring in adults aged 20–32 (1). While RRP can occur anywhere in the respiratory tract, the most common site for papillomas is the larynx (2). Patients with RRP can present with a variety of symptoms including coughing, wheezing and as the disease progresses, dyspnea and dysphonia. Current treatment goals focus on curing current and preventing future lesions, with the fundamental treatment being surgical debulking (3). Because of the high recurrence rate in aggressive RRP, patients are faced with a difficult clinical course which could include twice the amount of procedures as a nonaggressive patient and a lifetime cost of $500,000 (4).

RRP is caused by the human papilloma virus (HPV), a small virus with over 118 different subtypes, with the majority of RRP patients having types 6 and 11 (3). In general, patients with HPV type 11 tend to have more aggressive disease course (5). This is especially noticeable in pediatric patients where children with HPV type 11 have an increased risk for obstructive airway disease and an increased likelihood of using a tracheotomy to secure the airway (6–7). Interestingly, recent evidence has shown that almost five percent of the general population has evidence of HPV in their larynx. However not all of these cases develop into RRP and of those that do, even fewer develop into aggressive disease (8).

Gastroesophageal reflux disease (GERD) is a multifactorial pathologic condition characterized by mucosal damage of the esophageal epithelium by stomach acid. Respiratory complications of GERD include stridor, chronic cough, laryngeal irritation, obstructive apnea and possible squamous cell carcinoma (9). The link between GERD and RRP might be a contributing factor to the aggressiveness of the disease course (11). Furthermore, the medical management of GERD in patients with RRP has shown to decrease the rate of recurrence and the severity of RRP (10).

Our goal in this investigation is to validate GERD, as well as proton pump inhibitor (PPI) use, as a comorbidity for predicting clinically aggressive RRP.

Methods

Institutional Review Board approval was granted for this retrospective cohort study and records from the Center for Voice and Swallowing Disorders and the Department of Otolaryngology at the Medical College of Georgia were reviewed. Patients treated for RRP from 1998 to 2011 were identified and clinical and pathologic data, including age at disease presentation, gender, ethnicity, presence of comorbitides such as GERD, asthma and inhaled corticosteroid use, were recorded. The number of procedures defined as office-based argon-dye laser and surgical procedures under general anesthesia including microdebriderment and carbon dioxide laser treatment—in a consecutive 12-month span was recorded. The patients were then stratified according to clinically aggressive disease—defined as more than four procedures performed in 12 months, distal spread of the disease or the occurrence of laryngeal squamous cell carcinoma—or non-aggressive disease based on disease progression.

The primary endpoint was severity of RRP with or without the presence of GERD or PPI use. Statistical significance between demographics, presence of asthma or GERD, inhaled corticosteroid use and aggressive disease was determined using Fisher’s exact test. The secondary endpoint was severity of RRP with or without the presence of asthma. The number of procedures performed in patients with asthma and the age of onset of disease in those patients was compared using the Wilcoxon Rank-Sum test. All statistical analysis was done using SPSS 14.0 (SPSS Inc., Chicago, IL) and were two-tailed.

Results

The majority of patients (59%) with recurrent respiratory papillomatosis (RRP) also reported a history of gastroesophageal reflux disease (GERD). Of the patients with GERD, 19% had aggressive disease, compared to 44% without a history of GERD. Interestingly, despite both diseases being chronic inflammatory conditions, that was not a significant finding. However, when proton-pump inhibitor (PPI) therapy was factored in the relationship was clarified.

Among patients with no history of GERD, 28% were on PPI therapy compared to 100% of patients with history of GERD. Furthermore, there was a strong correlation between lack of PPI therapy and aggressive RRP as shown in Table 1.

Table 1. Association between aggressive RRP and PPI use

<table>
<thead>
<tr>
<th></th>
<th>Aggressive RRP</th>
<th>Non-aggressive RRP</th>
</tr>
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<tbody>
<tr>
<td>On PPI</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Not on PPI</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>p = 0.009 by Fisher exact test</td>
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Discussion

Although one explanation for our findings involves amelioration of acidic extra-esophageal reflux induced laryngeal tissue trauma, another possibility exists. Altmann et al demonstrated the presence of H+/K+-ATPase proton pump in human larynx (Figure 2) as well as lung tissue. This finding raises the possibility of a direct mechanism of action at the laryngeal tissue level, for PPI therapy. Further studies are needed to determine the exact mechanism of action.

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References