Predictors of Clinically Aggressive Recurrent Respiratory Papillomatosis

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Abstract

Objective: To determine possible predictive factors for clinically aggressive recurrent respiratory papillomatosis (RRP).

Study Design: Retrospective cohort study at a tertiary academic medical center.

Methods: Patients (adults and children) treated for RRP from 1998 to 2008 were identified using billing data and procedure logs. Cases were dichotomized into clinically aggressive versus non-aggressive disease. Aggressiveness was defined as: undergoing more than four procedures in twelve months, distal spread of disease, or transformation to squamous cell carcinoma.

Results: Forty-four patients with RRP were identified. Age ranged from 4 months to 81 years old with 6 pediatric and 38 adult patients. There were 22 males and 22 females. Maximum number of surgical procedures in one year ranged from 1 to 13 (mean 3.4). Six patients had distal spread of disease and one suffered malignant transformation. Thirteen patients had aggressive disease and 31 patients had non-aggressive disease. Five patients had asthma. Pediatric patients were more likely to have aggressive disease (67% versus 24%, p=0.05). There was no association between GERD and aggressive disease, however patients not on PPI therapy were more likely to have aggressive disease (62% versus 16%, p=0.009). There was a strong association between asthma and aggressive RRP, with 100% of asthma patients having aggressive disease versus 21% of non-asthma patients (p=0.001).

Conclusion: Asthma is associated with aggressive clinical course for RRP. Additional predictors of aggressive disease include lack of PPI use and pediatric disease onset. Patients with asthma may warrant closer clinical followup, and possible etiologic explanations for this finding are currently being investigated in our laboratory.

Introduction

RRP is the most common benign neoplasm of the larynx, and requires frequent surgical therapy resulting in over $109 million health care costs annually. RRP has been linked to the Human Papillomavirus (HPV) types 6 and 11. It is characterized by hyperplastic tissue growth in the upper respiratory tract. This condition causes hoarseness in early stages and can obstruct the airway if untreated. As the name infers, recurrence is characteristic of RRP. Some patients must undergo surgical treatment monthly, while others require much less frequent interventions. The clinical course of RRP is widely variable with some patients requiring frequent surgical intervention while others experience relatively benign disease progression. Pediatric patients with RRP typically require more frequent surgical interventions and have a more aggressive disease course. Increased epithelial proliferation and progression of several disease processes, including cancer, have been linked to chronic inflammation. In particular, HPV-caused cervical cancer has been shown to have significant dependence on chronic inflammation for progression to invasive cancer.

Hypothesis

Asthma as a comorbid illness is associated with clinically aggressive Recurrent Respiratory Papillomatosis.

Methods

A retrospective chart review was performed identifying patients with Recurrent Respiratory Papillomatosis from 1998 to 2008. Demographics and comorbidities were identified and recorded. The number of surgical treatments was recorded. Clinical parameters including asthma, GERD, medication use (oral contraceptives, inhaled corticosteroid, PPI) were recorded based on history. Aggressiveness was defined as indicated.

Aggressive RRP disease was defined as any:

- Distal spread of RRP disease
- More than four procedures in twelve months
- Transformation to malignancy (laryngeal carcinoma)

Results

Forty four unique patients were identified. Age ranged from three months to 81 years old with a median of 50 years. Six patients had disease onset <18 years (pediatric patients) with 38 adult patients. Pediatric patients were more likely to have aggressive disease (p=0.05). There was a strong association of aggressive disease with asthma (p=0.001). There was no association between GERD and aggressive RRP (p>0.05). Among non-GERD respiratory papillomatosis patients, however, those not on PPI therapy had more aggressive disease (p=0.005).

Conclusion

Based on these findings and a review of the literature, we would recommend that RRP patients be considered for PPI therapy unless contraindicated. Additionally, RRP patients with asthma may deserve closer clinical follow-up, but this will need to further investigated.

Discussion

We found a link between asthma, lack of PPI use, and clinically aggressive RRP. As our study was retrospective in nature, it is impossible to draw conclusions regarding etiology. We propose three possibilities that may explain this association. The first possibility is that asthma (possibly in combination with extraesophageal reflux) represents a chronic inflammatory process affecting the laryngeal epithelium, leading to more rapid epithelial growth and clinically aggressive disease. Asthma is a chronic inflammatory disease affecting the airway epithelium, characterized by perturbation of the immune system towards a Th2 response. Interestingly, both asthma and RRP may be disease states characterized by immune system perturbation towards a Th2 response. It is tempting to hypothesize that further promotion of a Th2-type immune response induced by asthma-related cytokine alterations may produce a more permissive tumor-stromal environment for RRP to progress. A second possibility is that inhaled corticosteroids (standard first-line therapy for asthma) may produce local immunosupression 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 reduced host cell-cycle control and increased cell proliferation.

Fig 1. Typical appearance of RRP involving the glottic larynx (true vocal folds)

Fig 2. RRP Aggressiveness compared to PPI use and history of asthma. Panel A shows patients on PPI therapy had less aggressive RRP compared to patients not on PPI therapy. Panel B shows patients with asthma were more likely to have aggressive RRP.

References


